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APPARATUS FOR, AND METHOD OF, VARYING THE
RATE OF FLOW OF FLUID ALONG A PATHWAY

5 Technical Field

This invention relates to an apparatus for and method of varying the rate of flow of a fluid along a pathway. More particularly, but not exclusively, the invention varies the rate of flow of fluid along a pathway in a wet chemistry analysis system.

10 Background Art

A common feature of all "wet chemistry" analysis or assay systems is that analyte, together with one or more reagents, usually passes through a series of processes or procedures. These include: mixing, reacting, incubating, filtering, decanting, metering and dividing. In short, some form of fluid handling is a common and important feature of most assay systems.

15 International Patent Application WO-A1-9419484 (Biocircuits Corporation) describes a disposable device for use in diagnostic assays and comprises a number of chambers and interconnecting pathways. Capillary valves are used to enhance control over fluid flow in the device. One type of capillary valve comprises a fluid flow capillary channel and a control capillary channel which intersect each other at right angles. The intersection disrupts fluid flow in the flow capillary channel when the control capillary is empty, but does not impede flow through the flow capillary channel when it is full. Thus, fluid flow through the device can be controlled by either filling or emptying the control capillary with liquid.

20 A similar disposable device is described in International Patent Application WO-A1-9727324 (David Sarnoff Research Center). This device uses valves and pumps for controlling the flow of fluid. The valves used may be of the plunger type such that the valve has a piston and plunger rod. The diameter of the plunger rods is typically of the order of 60 μm and the piston diameter is typically of the order of 200 μm .

25 In US Patent No. 5,278,079 (Enzymatics Inc.) a diagnostic device having capillary tubes is described. The capillary tubes contain a volume of water-expandable polymer which forms

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a seal in the tubes when it is in contact with an aqueous medium. However, once sealed, the capillary tubes cannot be easily reopened.

In conventional analysis techniques, fluid handling relies on precisely engineered fluid controllers such as valves, taps and fluid delivery systems. These fluid controllers are expensive and difficult to manufacture. They are therefore not appropriate for inclusion in disposable units due to their number and cost.

An aim of the present invention is to overcome the aforementioned problems by providing a means for varying the flow of fluid along a pathway.

Disclosure of Invention

According to a first embodiment of the invention there is provided a method of varying the rate of fluid flow along a pathway comprising the steps of: providing at least one recess located substantially adjacent the pathway; locating a plug of deformable material in the pathway so that the material substantially restricts the flow of fluid in the pathway; and changing the state of the deformable material so that at least a portion of the material passes into the at least one recess thereby permitting flow of the fluid along the pathway.

According to a second embodiment of the invention there is provided method of varying the rate of fluid flow along a pathway comprising the steps of: providing at least one recess located substantially adjacent the pathway; locating a volume of deformable material in the at least one recess; and changing the state of the deformable material so that at least a portion of the material passes into the pathway thereby substantially restricting flow of the fluid along the pathway.

According to a third embodiment of the invention there is provided a method of varying the rate of fluid flow along a pathway comprising the steps of: providing a pathway; locating a volume of deformable material in the pathway so that it substantially restricts the flow of fluid along the pathway; and changing the state of the deformable material so that at least a portion of the material passes along a predetermined path thereby permitting flow of the fluid along the pathway.

According to a fourth embodiment of the invention there is provided a method of varying the rate of fluid flow along a pathway comprising the steps of: providing a pathway; locating a volume of deformable material in the pathway so that it substantially permits the flow of fluid along the pathway; and changing the state of the deformable material so that at least a portion of the material passes along a predetermined path thereby substantially restricting flow of the fluid along the pathway.

Preferably the predetermined path is defined by one or more regions that repels or attracts the deformable material. A region having such a property is hereinafter referred to as being hydrophobic.

The state of the deformable material may be changed by applying to the deformable material (i) heat, (ii) pressure, (iii) uv radiation, (iv) light, (v) ultrasonic energy or a combination of any of (i) to (v).

According to a further embodiment of the invention there is provided an apparatus for varying the rate of fluid flow along a pathway, the apparatus including at least one pathway and a volume of deformable material disposed within the pathway whereby, in use, a change of state of the deformable material causes a change of the rate of fluid flow along the pathway.

According to another embodiment of the invention there is provided an apparatus for varying the rate of fluid flow along a pathway, the apparatus including at least one pathway and a volume of deformable material disposed adjacent the pathway whereby, in use, a change of state of the deformable material causes a change of the rate of fluid flow along the pathway.

The apparatus may also include at least one chamber in fluid connection with one or more pathways. A volume of deformable material may be disposed within the at least one chamber.

At least one recess capable of receiving deformable material is preferably located substantially adjacent the at least one pathway. The at least one recess may have an opening which acts as a vent in order to permit the flow of gas therethrough.

5 The apparatus may also include at least one hydrophobic region. Thus the flow of material is guided along a predetermined path and discouraged from contacting other regions of the pathway, chamber, or device.

The apparatus may include means for the supply and/or removal of heat from the apparatus in order to increase or decrease the rate of change of state of the deformable material. 10 When heat (or other form of energy) is applied to a region of the apparatus containing the deformable material, the material may change its position, size, state or function. This causes a rate of change in the fluid flow in the pathway. Thus a pathway which is initially obstructed becomes unobstructed, and vice versa.

15 Heater elements may be printed onto the apparatus or a heating tool may be used to apply heat to local areas of the apparatus. Alternatively, heat may be applied to or removed from larger regions of the apparatus, or to a device which includes the apparatus. For example, by dipping into a water bath, heating with an external heater, or by a Peltier.

20 The apparatus may also include means for the supply of pressure, uv radiation, light, ultrasonic energy, or other suitable means for changing the state of the deformable material.

25 The deformable material may be a thermally activated material. Preferably the thermally activated material is wax, contains or is a polymer such as polypropylene polystyrene, a wax/polymer mix, a metal such as Indium, or any other suitable low melting point material that changes its state on application of heat, and on cooling. The terms thermally activated material and wax are hereinafter used interchangeably.

30 In summary, fluid flow along a pathway of the apparatus is varied by way of valves, or clamps, which are preferably formed from a deformable material. The valves and clamps

may be opened and/or closed upon the application of heat, pressure, or other suitable means. The valves and clamps may also be known as gates. Hereinafter, a gate that opens a pathway to the flow of fluid on application of heat is known as a heat openable gate. A gate that closes a pathway to the flow of fluid on application of heat is known as a heat closable gate.

5 closable gate.

One example of a heat openable gate has thermally activated material situated in the pathway so as to enable the material in its melted state to flow into at least one recess substantially adjacent the pathway. Air (or other gas) is displaced from the recess by the material and exits through a vent. A type of heat closable gate has thermally activated material situated in at least one recess substantially adjacent the pathway. As the material in its melted state flows from the recess into the pathway, it is replaced by air (or other gas) via the vent.

10 15 Alternatively, (or in addition to the material being situated in at least one recess), the material may be situated in the fluid pathway such that the pathway is either substantially or partially obstructed. If the thermally activated material is substantially obstructing the pathway, then the pathway may be opened to the flow of fluid by applying heat to the material. This is a form of heat openable gate. However, if the material is situated so as not to, or only partially, obstruct the flow of fluid, on application of heat the material melts 20 and flows so as substantially obstruct the pathway. This is a form of heat closable gate.

In a further alternative embodiment, thermally activated material may be arranged to contact at least two points on inner surfaces of the apparatus, forming a clamp. Clamps 25 may be situated in chambers. Upon application of heat to a clamp, the clamp melts, and surfaces of the chambers are separated. Thus a pressure differential is provided to drive fluid along pathways and into, or from, chambers.

30 Preferably at least one surface contained within the apparatus is resiliently deformable. This is advantageous because it means that if the surfaces are constructed from sufficiently pliable materials, pressure may be applied to a surface, and the surfaces will return to their original state.

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Pathways may contain a volume of material so that upon application of pressure, a rate of change of fluid flow in the pathway occurs. The material may be thermally activated. Thus for a heat closable pathway, a tool may be used to seal the pathway by connecting the upper and lower surfaces with the thermally activated material. Thermally activated material may not be required if the upper and lower surfaces of the pathway may be directly connected to one another. For a heat openable pathway, a tool may make a channel in the wax contained in the pathway. When this occurs the resiliently deformable material of the pathway returns to a previous state. Pathways opened in this way may be resealed by heating and subsequent cooling of the wax.

10 Preferably the volumes of deformable material may be accessed independently and sequentially to precisely control the path of fluid flow in the apparatus.

Valves and clamps may be single use structures, or may be reusable.

15 The invention may be incorporated into a chemical assay device. The assay device preferably has at least one chamber in fluid connection with at least one pathway, the pathway being adapted to allow fluid to flow to or from said chamber, characterised in that there is provided a volume of deformable material in the pathway whereby, in use, a change of state of the deformable material causes a change of the rate of fluid flow along 20 the pathway.

The deformable material may be situated in the pathway such that the pathway is substantially obstructed or, alternatively, the material may be situated in the pathway such 25 that the pathway is only partially obstructed.

At least one recess may be located substantially adjacent the pathway, the recess being capable of receiving the deformable material.

30 According to another embodiment of the invention, the assay device preferably has at least one chamber in fluid connection with at least one pathway, the pathway being adapted to allow fluid to flow to or from said chamber, characterised in that there is provided a volume of deformable material situated in a recess, the recess being located substantially

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adjacent the pathway whereby, in use, a change of the deformable material causes a change of the rate of fluid flow along the pathway.

An opening may be provided in the recess which acts as a vent.

5 The chamber may comprise a deformable envelope and at least two points on the envelope may be connected by way of a volume of deformable material.

A region of the device may have at least one hydrophobic portion so that the flow of the
10 deformable material is guided along a predetermined path.

Preferably the deformable material is thermally deformable. The material may, however,
be mechanically deformable.

15 The device may include heating means for melting the thermally deformable material. The device may also include means for removing heat such as, for example, a heat sink. Heat may selectively be applied and/or removed from individual wax gates and/or clamps.

20 Preferably at least one surface defined by or in the device is resiliently deformable so that the wax gates and/or clamps may be mechanically deformed.

The device may have at least one component from the set of: an inlet port, a reaction chamber, a waste depot, a filter chamber, an infinity capture and processing chamber, a wash solution/reagent reservoir, an array of metered readout cells, and a breather tube.

25 The assay device is usually rectangular, but other shapes are equally viable, such as discs or hexagons. Depths of fluid pathways and chambers may be sufficiently narrow to allow filling by capillary action (say 0.02 to 0.2 mm). Pathways may be wider (of the order of a millimeter) where the fluid flow is to be propelled by gravity, a pressure impulse, or centrifugal force, or an inertial force. The aforementioned dimensions are consistent with 30 processing fluid samples in the range of approximately 30 to 50 microlitres, and are given by way of example only.

According to a further embodiment of the invention there is provided a method of manufacturing an assay device, the method including the steps of: a) defining at least one fluid pathway on a substrate; b) defining at least one reaction chamber on a substrate; c) forming at least one component composed of a deformable material in the device; and d) bonding together at least two substrates to form the device.

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The body of the assay device is preferably formed from a polymer or from a combination of materials including glass, ceramics, or metal. Construction may involve injection moulded components, and/or the joining together of a number of laminae. Pathways and chambers in the assay device may be formed in a plane defined between upper and lower planar sheets. Pathways and chambers may be formed by printing, etching, ablation, cutting of the substrate, moulding of a substrate, or a combination of these. More complex structures may be realised by building up laminae and providing vias for the flow of fluids between adjacent levels.

Bonding of upper and lower portions of the device is critical for its operation. Bonding can be achieved by means of screen printed adhesives containing for example spacer balls, by cut adhesive gasket materials, by heating sealing, by uv curing, by mechanical fixing, by ultrasonic bonding, or by using a porous-gasket technique, for example as described in US-A-4,865,716.

The assay device may include one or more of the aforementioned gates, valves or clamps. Preferably each individual gate, valve and/or clamp may be accessed independently one from another.

Wax gates and clamps may also be printed using molten wax or wax dissolved in a solvent, by injection of molten wax into the device using feeder tubes, by etching of the device, or by placing individual wax elements within the apparatus using pick and place equipment.

Provision may be made for fluid overflow lines, for collection of waste, and for opening and sealing of the device at stages from start of use until disposal.

Brief Description of Figures

Embodiments of the invention will now be described by way of examples, and with reference to the accompanying Figures in which:-

- 5 Figure 1 is a schematic plan view of a chemical assay device incorporating the invention;
- Figure 2a is a plan view of a pathway having an initially open wax gate, where wax is situated in recesses adjacent the pathway;
- Figure 2b shows a plan view of the pathway of Figure 2a, where the wax gate has been closed upon the application of heat to the gate;
- 10 Figure 3a shows a plan view of a pathway having an initially open wax gate, where a volume of wax is situated in the pathway;
- Figure 3b shows a plan view of the pathway of Figure 3a, where the wax gate has been closed upon the application of heat to the gate;
- 15 Figure 4a shows a plan view a pathway having an initially open wax gate, where a volume of wax is situated in the pathway;
- Figure 4b shows a cross-section of the pathway of Figure 4a;
- 20 Figure 4c shows a cross-section of the pathway of Figure 4a, the pathway having been closed on application of heat and pressure;
- Figure 5a shows a plan view of a pathway having an initially closed wax gate, where wax is situated in the pathway, and recesses adjacent the pathway;
- 25 Figure 5b shows a plan view of the pathway of Figure 5a, where the wax gate has been opened upon the application of heat to the gate, wax having flowed into the recesses adjacent the pathway;
- Figure 6a shows a plan view of a pathway having an initially closed wax gate, where a volume of wax is situated in the pathway;
- 30 Figure 6b shows a plan view of the pathway of Figure 6a, where the wax gate has been opened upon the application of heat to the gate;

Figure 7a shows a cross-section of a pathway having a wax gate which has been closed, and a heating tool;

Figure 7b shows a cross-section of the pathway of Figure 7a, where the pathway has been reopened to the flow of fluid upon application of heat and pressure;

5 Figure 7c shows a plan view of Figure 7b;

Figure 8a shows a plan view of a wax clamp used in a chamber, in which the clamp may be initially closed or open;

Figure 8b shows a cross-section of an deflated chamber having a wax clamp;

10 Figure 8c shows a cross-section of an inflated chamber having a wax clamp;

Figure 9a shows a plan view of a chamber containing a gas generating mixture in fluid connection with a pathway having an initially closed wax gate;

15 Figure 9b shows a plan view of the chamber of Figure 9a having an opened wax gate where fluid has flowed into the chamber (under capillary action or external pressure), and is in contact with the gas producing material contained within the chamber;

Figure 9c shows a plan view of the chamber of Figure 9a where fluid has been driven out of the chamber by a gas; and

Figure 9d shows a cross-section of the chamber and connecting pathway of Figure 9a.

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Detailed Description of Preferred Embodiments

The embodiments of the invention shown in Figures 2 to 9 may be incorporated into the chemical assay device of Figure 1, or they may be included in other types of assay (or other) devices.

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Referring to Figure 1, there is shown a chemical assay device 10 for analysis of blood, or other biological fluid. End products of a reaction or assay may be detected using optical methods. For example, a colour change may be detected by a photo-diode, or a fibre-optic system, or visually. The device has an area typically about 50 cm² and is 3 to 10 millimetres thick. The device 10 may be significantly larger or smaller depending on the complexity of the processes to be carried out and the volumes of fluids to be processed. In this particular embodiment, the assay device 10 is configured to carry out an

immunological assay and this will be described so as to illustrate a method of operation of the invention.

Assay device 10 comprises a generally square, substantially planar substrate in which a number of chambers are interconnected by pathways. Fluid control in the device 10 is by way of wax gates and clamps, which are shown in Figure 1 in their initial (open or closed) states.

The device 10 includes an inlet port 12 in fluid connection with a reaction (e.g., lysing) chamber 14 via a pathway 12a. Chamber 14 leads to waste depot 16 and filter chamber 18 via separate fluid channels 14a and 14b respectively. Filter chamber 18 is in fluid connection with chambers 22 and 24 via respective fluid channels 18a and 18b, and with processing chamber 20. Chamber 22 is initially filled with a wash solution, and chamber 24 is filled with an eluent which is used to displace material from processing chamber 20.

Processing chamber 20 is connected to waste depot 16 via a channel 20a. Channel 20a leads to an array of metered read-out cells 26, 28, 30 and 32. Air from read-out cells 26 to 32 exits into channel 16a. A channel 16b is provided and links channels 20a and 16a. The operation of one of the metered readout cells will now be explained with reference to readout cell 26 of Figure 1.

A region of the analysis area of device 10 comprises a large-bore inlet port 26a leading to a fixed-volume cell 26, which in turn is connected to a narrow-bore outlet tube 26b. Tube 26b leads to pathway 16a, and ultimately to waste depot 16. The structure comprising parts 26a, 26 and 26b has a fluid impedance which is dependent on the amount of fluid therein. Fluid can flow freely into the cell until the narrow-bore section is reached, at which stage the force needed to continue driving the fluid into the cell is greatly increased. At this point the fluid, which flows most readily along the path of least resistance, diverts to the conduit leading to the next cell (28 in this case), and so on. Thus each of the cells 26, 28, 30, 32 is filled in turn, and the volume of fluid entering each cell can be controlled.

Chamber 20 is also connected to chamber 38 via a fluid pathway 20b, and chamber 38 leads to chamber 40. Chambers 38 and 40 both contain wax clamps. Both chambers 38 and 40 are initially deflated.

- 5 Waste depot 16 connects to breather tube 13 via pathway 16c, and reservoir 22 leads to breather tube 11 via pathway 22a. Breather tubes 11 and 13 ensure that fluid moves freely within the device. Also tubes 11 and 13, when connected to non-critical regions, ensure that any excess fluid does not interfere with any on-going analysis.
- 10 Reservoir 24 is connected to chamber 42 via pathway 24a. Chamber 42 is pre-filled with a dry mixture which, when in contact with a liquid, produces a gas. This is shown diagrammatically in Figure 9.

Wax gates are situated in fluid pathways in order to control flow of fluid between the chambers. In Figure 1, gates are shown in their initial states. For example, fluid flow is initially obstructed at gate 34, whereas initially fluid is allowed to flow freely through gate 36.

- 20 Referring again to Figure 1, a typical sequence of events for an immunological assay is now described. A blood sample (not shown) is injected into the assay device via inlet port 12. Blood fills reaction chamber 14 by capillary action and/or hydrostatic pressure, and excess blood enters the waste depot 16 via pathway 14a. The blood remains in chamber 14 for as long as is required for cell lysing to occur with a reagent. The reagent is introduced into this chamber in a predetermined dose during the manufacture of the device. Heat is then applied to gates 44, 46 and clamp 48 in order to close gate 44, open gate 46, and release clamp 48 thereby actuating partial vacuum chamber 38.
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The lysed blood is then urged through filter chamber 18 by way of a partial vacuum, and serum fills processing chamber 20. An antigen in the blood serum then bonds to an antibody which has been tagged onto, for example, glass or ceramic beads (not shown). The beads are pre-dosed and introduced in chamber 20 at the manufacturing stage.

The serum is then washed from the glass beads in chamber 20 by activating heaters at gates 50, 52 and 54, and clamp 56. A partial vacuum in chamber 40 draws wash fluid from chamber 22 through chamber 20 leaving the antigen bound to the particles in chamber 20. Waste wash solution and serum enter chambers 38 and 40.

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The next step is elution. Activating heaters placed at gates 57, 58, 60, 36, 34 and 62 allow the fluid in the reagent reservoir 24 to wet a gas producing powder. Fluid is then driven by the gas through chamber 20 towards analysis cells 26, 28, 30 and 32. As eluent from reservoir 24 passes through chamber 20, antigen is released from the beads and carried in the eluent to the analysis cells. These cells contain reagents such as enzyme systems which react with the antigen, causing either a colour change in the solution, or a change in fluorescence. Any recognised method of optical analysis can then be used for detection and measurement of end products of the reactions. Once cells 26, 28, 30 and 32 are filled, resistance to fluid flow increases in the narrow exit channels 26b, 28b, 30b, and 32b.

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Excess fluid is then expelled to waste depot 16 through channel 16b.

Finally, activating heaters at gates 66, 68 and 70 seal the fluids within the device for hygienic disposal.

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Further embodiments of the invention are described now with reference to Figures 2 to 9 inclusive.

Figure 2 shows a plan view of a section of a pathway having a wax gate 73 that closes the pathway to the flow of fluid on application of heat. A volume of wax is contained in recess 72. Pathway 75 has a region of hydrophobicity 76 in order to guide the flow of wax. Upon application of heat to gate 73, the wax melts and flows (guided by the hydrophobic region) into the fluid pathway to obstruct the flow of fluid therein. Air enters through inlet 74 and replaces the wax in recess 72. Thus air prevents flowback of the molten wax. As the wax cools, fluid flow along the pathway becomes obstructed.

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In Figure 3 a plan view of a section of pathway having a wax gate 77 is shown. Gate 77 closes pathway 75 to the flow of fluid on application of heat to the gate. A volume of wax 78 is situated in the path of the fluid, only partially obstructing the fluid flow. Upon

application of heat to the gate, the wax melts and flows to block the pathway guided by the area of hydrophobicity 76. As the wax cools fluid flow along the pathway becomes obstructed.

- 5 Figure 4 shows another form of heat closable pathway. A volume of wax 78 is situated in pathway 75, only partially obstructing the flow of fluid. In order to block the channel, a moveable heat sealing tool 80 is used to apply both pressure and heat, completely sealing the channel. This form of gate requires that at least one sheet forming the pathway is formed from deformable material. If the deformable material can be directly sealed to the 10 second sheet (by heat, pressure or otherwise), then wax is not required.

Figures 5, 6 and 7 all represent forms of heat openable pathways, that is, wax gates that are initially closed to fluid flow in the pathway.

- 15 Figure 5 shows a plan view of a section of a pathway 75 having a gate 79 that opens the pathway to the flow of fluid on application of heat to the gate. A volume of wax is situated in the pathway between two recesses 72. The recess has a region of hydrophobicity 76 in order to guide the flow of wax. Upon application of heat to the gate, the wax melts and flows into the recess. Air exhausts via inlet 74 and is replaced by the wax in the recess, preventing flowback of the molten wax. As the wax cools the fluid pathway opens.
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- Referring to Figure 6, there is shown a plan view of a section of pathway 75 having another form of wax gate 81. The gate opens the pathway to the flow of fluid on application of heat to the gate. A volume of wax 78 is situated in the path of the fluid preventing fluid flow. Upon application of heat to this wax gate, the wax melts and flows in the pathway guided by the area of hydrophobicity 76. As the wax cools, the fluid pathway permits fluid to flow along the pathway.
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- Figure 7 shows another heat openable gate situated in pathway 75. A volume of wax 78 is situated in the pathway, obstructing the flow of fluid. In order to open the pathway to allow the flow of fluid, a moveable heat sealing tool 80 is used to apply both pressure and heat to the pathway. The shape of this heat sealable tool allows the wax to be deformed, forming a channel in the wax. This type of gate requires that at least one sheet forming the pathway is

deformable and resilient, so that the sheet may return to its original state and leave the pathway open.

In addition to the aforementioned wax valves, components to actuate fluid flow may be required. Capillary action may be used to provide some fluid movement, and this can be extended by opening further fillable or absorbent areas or by opening valves of the types previously described. However, greater flexibility is achieved by employing structures capable of generating pressure differentials, and these are shown in Figures 8 and 9.

- 10 Figure 8 shows a chamber 38 containing a wax clamp 78. Changing the shape and volume of chamber 38 provides a pressure differential to drive (or suck) fluid in the connected pathways and chambers. Two sheets of synthetic plastics material 37a and 37b are fixed together using a volume of wax 78 in order to produce a deflated chamber 38. Upon application of heat, wax clamp 78 melts. This allows the surfaces of chamber 38 to separate thereby inflating the chamber. This results in a pressure change and fluid is sucked through interconnecting pathways. Chamber 38 may be returned to its deflated state by the application of an external pressure (shown in the direction of arrow A) and by heating the wax. As the wax cools, the deformable surfaces are fixed together.
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- 20 Figure 9 shows a further means of generating pressure in order to drive the flow of fluid. Figure 9 shows a chamber 88 connected to a pathway having a closed wax gate 86. The chamber contains a dry gas generating mixture 82, for example sodium bicarbonate with tartaric acid. On applying heat to the wax gate 86, the wax flows to unblock the pathway 85. A solution 84 flows into the chamber 88, wetting the gas generating mixture and causing the generation of a gas. The gas increases the pressure inside the chamber, ejecting the liquid that has flowed into the chamber and propelling it along one or more interconnecting pathways. In addition to the gas generating mixture, an inert absorbent material may be included in the chamber, or the chamber may be filled with capillary matting which acts as a wick.
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- 30 The invention has been described by way of a number of embodiments, and it will be appreciated that variation may be made to these embodiments without departing from the scope of the invention.

Claims

- 5 1. A method of varying the rate of fluid flow along a pathway (75) comprising the steps of: providing at least one recess (72) located substantially adjacent the pathway (75); locating a plug of deformable material (78) in the pathway so that the material substantially restricts the flow of fluid in the pathway; and changing the state of the deformable material so that at least a portion of the material passes into the at least one recess thereby permitting flow of the fluid along the pathway.
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- 15 2. A method of varying the rate of fluid flow along a pathway comprising the steps of: providing at least one recess (72) located substantially adjacent the pathway (75); locating a volume of deformable material (78) in the at least one recess; and changing the state of the deformable material so that at least a portion of the material passes into the pathway thereby substantially restricting flow of the fluid along the pathway.
- 20 3. A method of varying the rate of fluid flow along a pathway (75) comprising the steps of: providing a pathway (75); locating a volume of deformable material (78) in the pathway so that it substantially restricts the flow of fluid along the pathway (75); and changing the state of the deformable material so that at least a portion of the material (78) passes along a predetermined path thereby permitting flow of the fluid along the pathway.
- 25 4. A method of varying the rate of fluid flow along a pathway (75) comprising the steps of: providing a pathway (75); locating a volume of deformable material (78) in the pathway so that it substantially permits the flow of fluid along the pathway; and changing the state of the deformable material so that at least a portion of the material (78) passes along a predetermined path thereby substantially restricting flow of the fluid along the pathway.
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5. A method according to claim 3 or claim 4 wherein the predetermined path is defined by one or more hydrophobic regions (76).

6. A method according to claims 1 to 5 whereby the state of the deformable material (78) is changed by applying to said material (i) heat, (ii) pressure, (iii) uv radiation, (iv) light, (v) ultrasonic energy or a combination of any of (i) to (v).
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7. Apparatus for varying the rate of fluid flow along a pathway (75), the apparatus including at least one pathway (75) and a volume of deformable material (78) disposed within the pathway whereby, in use, a change of state of the deformable material causes a change of the rate of fluid flow along the pathway.
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8. Apparatus for varying the rate of fluid flow along a pathway (75), the apparatus including at least one pathway (75) and a volume of deformable material (78) disposed adjacent the pathway whereby, in use, a change of state of the deformable material causes a change of the rate of fluid flow along the pathway.
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9. Apparatus according to claim 7 or 8 further including at least one chamber in fluid connection with the pathway.
10. Apparatus according to claim 9 wherein a volume of deformable material is disposed within the chamber.
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11. Apparatus according to any of claims 7 to 10 wherein at least one recess (72) capable of receiving deformable material is located substantially adjacent the pathway (75).
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12. Apparatus according to claim 11 wherein the at least one recess (72) has an opening (74) which acts as a vent in order to permit the flow of gas therethrough.
13. Apparatus according to any of claims 7 to 12 including at least one hydrophobic region (76) in order to guide fluid along a predetermined path.
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14. Apparatus according to any of claims 7 to 13 including means for the supply and/or removal of heat from the apparatus in order to increase or decrease the rate of change of state of the deformable material.

15. Apparatus according to any of claims 7 to 14 including means for the supply of (i) pressure, (ii) uv radiation, (iii) light, (iv) ultrasonic energy or a combination of any of (i) to (iv) to the apparatus in order to change the state of the deformable material.

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16. Apparatus according to any of claims 7 to 15 wherein the deformable material (78) includes a polymer.

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17. Apparatus according to any of claims 7 to 15 wherein the deformable material (78) includes polypropylene polystyrene.

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18. An assay device (10) having at least one chamber (14) in fluid connection with at least one pathway (14a, 14b), the pathway being adapted to allow fluid to flow to/from said chamber (14), characterised in that there is provided a volume of deformable material (46) in the pathway (14b), whereby, in use, a change of state of the deformable material causes a change of the rate of fluid flow along the pathway.

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19. An assay device (10) having at least one chamber (14) in fluid connection with at least one pathway (14a, 14b) the pathway being adapted to allow fluid to flow to/from said chamber (14), characterised in that there is provided a volume of deformable material (44) situated in a recess, the recess being located substantially adjacent the pathway (14a), whereby, in use, a change of state of the deformable material causes a change of the rate of fluid flow along the pathway.

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20. A device (10) according to claim 18 wherein there is at least one recess located substantially adjacent the pathway (14b).

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21. A device (10) according to any of claims 18 to 20 wherein an opening is provided, the opening acting as a vent to or from the recess.

22. A device (10) according to claim 18 wherein the deformable material (46) is situated in the pathway (14b) such that the pathway is partially obstructed.

23. A device (10) according to any of claims 18 to 22 wherein the chamber (38,40) comprises a deformable envelope and at least two points of the envelope are connected by way of a volume of deformable material (48,56).
- 5 24. A device (10) according to any of claims 18 to 23 wherein a region of the device has at least one hydrophobic portion so that the flow of the deformable material is guided along a predetermined path.
- 10 25. A device (10) according to any of claims 18 to 24 wherein the deformable material is thermally deformable.
- 15 26. A device (10) according to any of claims 18 to 24 wherein the deformable material is mechanically deformable.
- 20 27. A device (10) according to any of claims 18 to 26 further including heating means (80).
- 25 28. A device (10) according to any of claims 18 to 27 further including a means for removing heat.
- 30 29. A device (10) according to any of claims 18 to 28 wherein the at least one surface defined by or in the device is resiliently deformable.
- 35 30. A device (10) according to any of claims 18 to 29 wherein a plurality of volumes of deformable material are provided, each volume being accessible independently one from another.
- 40 31. A device (10) according to any of claims 18 to 30 having at least one component from the set of: an inlet port (12), a reaction chamber (14), a waste depot (16), a filter chamber (18), an infinity capture and processing chamber (20), a wash solution/reagent reservoir (22), an array of metered readout cells (26,28,30,32), and a breather tube (11, 13).

32. A device (10) according to any of claims 18 to 31, in which heat is selectively applied to one or more of the volumes of the deformable material.
33. A device (10) according to any of claims 18 to 32, in which heat is selectively removed from one or more volumes of the deformable material.
- 5 34. A device (10) according to any of claims 18 to 33, in which pressure is selectively applied to at least one region contained within the device.
- 10 35. A method of manufacturing an assay device (10), including the steps of: a) defining at least one fluid pathway (14a) on a substrate; b) defining at least one reaction chamber (14) on a substrate; c) forming at least one component composed of a deformable material (44) in the device; and d) bonding together at least two substrates to form the device (10).
- 15 36. A method of manufacturing the device (10) according to claim 35, wherein the at least one fluid pathway (14a) may be formed by: a) printing, b) etching, c) ablation, d) use of a mould, e) cutting, or a combination of any of steps a) to e).
- 20 37. A method of manufacturing the device (10) according to claim 35, wherein the at least one reaction chamber (14) is formed by: a) printing, b) etching, c) ablation, d) use of a mould, e) cutting, or a combination of any of steps a) to e).
- 25 38. A method of manufacturing the device (10) according to claim 35, wherein the at least one component (44) composed of a deformable material is formed by: a) printing of the deformable material onto the substrate, b) etching, c) pick-and-placing of components, d) injection of molten material into device using feeder tubes, or a combination of steps a) to d).
- 30 39. A method of manufacturing the device (10) according to claim 35, wherein the at least one substrate is bonded by: a) adhesives, b) curing, c) mechanical fixing, d) heating, e) anodic bonding, or a combination of steps a) to e).

40. Apparatus substantially as described herein with reference to Figures 2 to 9.

41. A device (10) substantially as described with reference to Figure 1.

5 42. A method of performing chemical analysis substantially as described with reference to
the Figures.

43. A method of varying the rate of fluid flow along a pathway substantially as described
herein with reference to the Figures.

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APPARATUS FOR, AND METHOD OF, VARYING THE
RATE OF FLOW OF FLUID ALONG A PATHWAY

5 Technical Field

This invention relates to an apparatus for and method of varying the rate of flow of a fluid along a pathway. More particularly, but not exclusively, the invention varies the rate of flow of fluid along a pathway in a wet chemistry analysis system.

10 Background Art

A common feature of all "wet chemistry" analysis or assay systems is that analyte, together with one or more reagents, usually passes through a series of processes or procedures. These include: mixing, reacting, incubating, filtering, decanting, metering and dividing. In short, some form of fluid handling is a common and important feature of most assay

15 systems.

International Patent Application WO-A1-9419484 (Biocircuits Corporation) describes a disposable device for use in diagnostic assays and comprises a number of chambers and interconnecting pathways. Capillary valves are used to enhance control over fluid flow in the device. One type of capillary valve comprises a fluid flow capillary channel and a control capillary channel which intersect each other at right angles. The intersection disrupts fluid flow in the flow capillary channel when the control capillary is empty, but does not impede flow through the flow capillary channel when it is full. Thus, fluid flow through the device can be controlled by either filling or emptying the control capillary with

25 liquid.

A similar disposable device is described in International Patent Application WO-A1-9727324 (David Sarnoff Research Center). This device uses valves and pumps for controlling the flow of fluid. The valves used may be of the plunger type such that the

30 valve has a piston and plunger rod. The diameter of the plunger rods is typically of the order of 60 μ m and the piston diameter is typically of the order of 200 μ m.

In US Patent No. 5,278,079 (Enzymatics Inc.) a diagnostic device having capillary tubes is described. The capillary tubes contain a volume of water-expandable polymer which forms

AMENDED CLAIMS

[received by the International Bureau on 27 July 1999 (27.07.99);
original claims 1-43 replaced by new claims 1-52 (7 pages)]

1. An assay device (10) having at least one chamber (14) in fluid connection with at least one pathway (14a, 14b), the pathway being adapted to allow fluid to flow to/from said chamber (14), characterised in that there is provided a volume of deformable material (46) in the pathway (14b), which, in use, changes its state so as to cause a change of the rate of fluid flow along the pathway.
2. An assay device (10) having at least one chamber (14) in fluid connection with at least one pathway (14a, 14b) the pathway being adapted to allow fluid to flow to/from said chamber (14), characterised in that there is at least one recess located substantially adjacent the pathway and, situated in the recess, there is provided a volume of deformable material (44) which, in use, changes its state so as to cause a change of the rate of fluid flow along the pathway.
3. An assay device (10) according to claim 1 wherein there is at least one recess located substantially adjacent the pathway (14b).
4. An assay device (10) according to any of claims 1 to 3 wherein an opening is provided, the opening acting as a vent to or from the recess.
5. An assay device (10) according to claim 1 wherein the deformable material (46) is situated in the pathway (14b) such that the pathway is partially obstructed.
6. An assay device (10) according to any of claims 1 to 5 wherein the chamber (38,40) comprises a deformable envelope and at least two points of the envelope are connected by way of a volume of deformable material (48,56).
7. An assay device (10) according to any of claims 1 to 6 wherein a region of the device has at least one hydrophobic portion so that the flow of the deformable material is guided along a predetermined path.
8. An assay device (10) according to any of claims 1 to 7 wherein the deformable material is thermally deformable.
9. An assay device (10) according to any of claims 1 to 7 wherein the deformable material is mechanically deformable.

10. An assay device (10) according to any of claims 1 to 9 further including heating means (80).
11. An assay device (10) according to any of claims 1 to 10 further including a means for removing heat.
12. An assay device (10) according to any of claims 1 to 11 wherein the at least one surface defined by or in the device is resiliently deformable.
13. An assay device (10) according to any of claims 1 to 12 wherein a plurality of volumes of deformable material are provided, each volume being accessible independently one from another.
14. An assay device (10) according to any of claims 1 to 13 having at least one component from the set of: an inlet port (12), a reaction chamber (14), a waste depot (16), a filter chamber (18), an infinity capture and processing chamber (20), a wash solution/reagent reservoir (22), an array of metered readout cells (26,28,30,32), and a breather tube (11, 13).
15. An assay device (10) according to any of claims 1 to 14, in which heat is selectively applied to one or more of the volumes of the deformable material.
16. An assay device (10) according to any of claims 1 to 15, in which heat is selectively removed from one or more volumes of the deformable material.
17. An assay device (10) according to any of claims 1 to 16, in which pressure is selectively applied to at least one region contained within the device.
18. An assay device (10) having: a) at least one chamber (14) in fluid connection with at least one pathway (14a, 14b), the at least one pathway being adapted to allow fluid to flow to/from said at least one chamber (14); b) a volume of deformable material (46) situated in the pathway (14b) which, in use, changes its state so as to cause a change of the rate of fluid flow along the pathway; and c) at least one hydrophobic portion which defines a path along which the deformable material is guided.

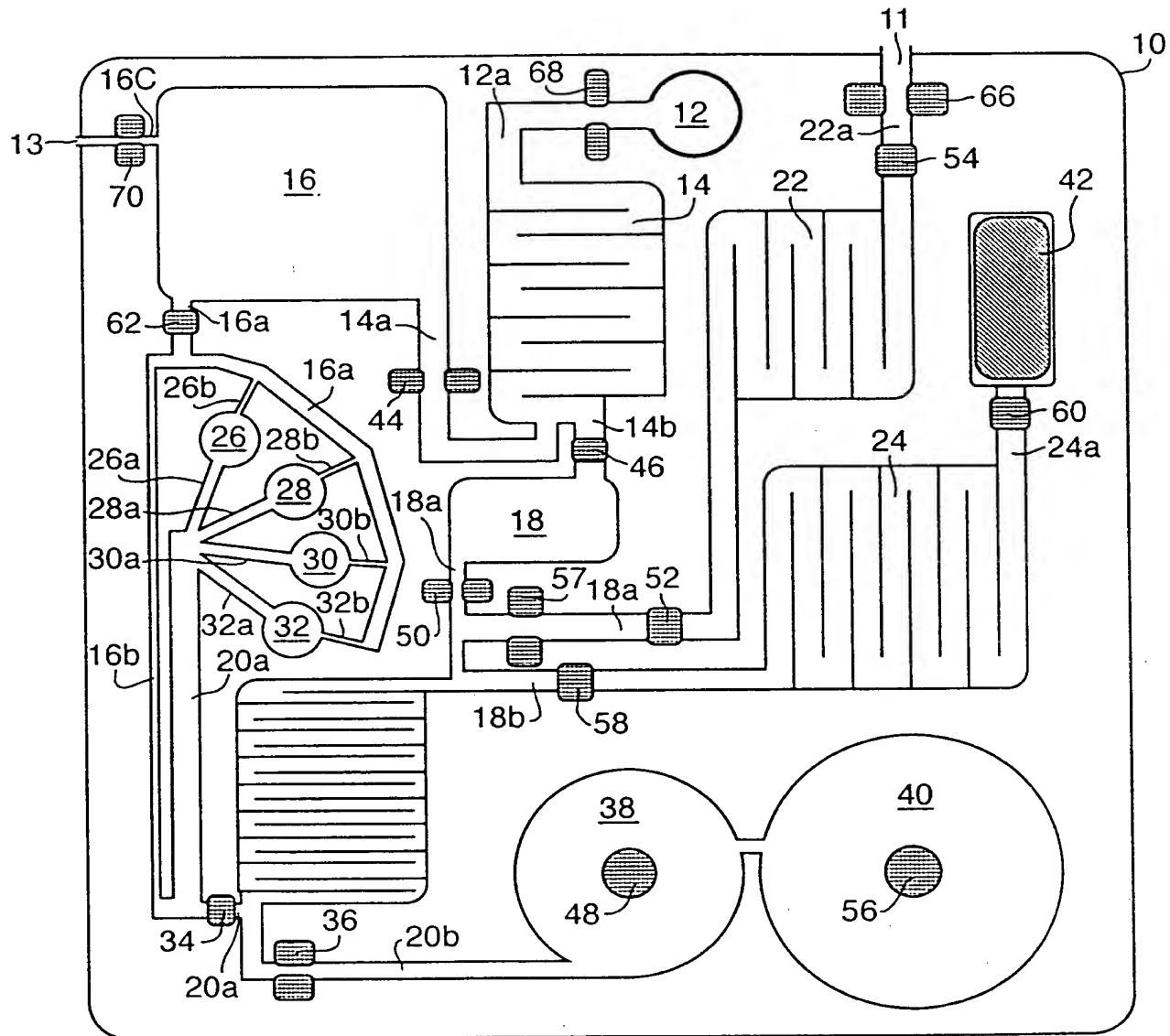
19. An assay device (10) having: a) at least one chamber (14) in fluid connection with at least one pathway (14a, 14b), the at least one pathway being adapted to allow fluid to flow to/from said at least one chamber (14); b) at least one recess located substantially adjacent the pathway; c) a volume of deformable material (44) situated in the recess which, in use, changes its state so as to cause a change of the rate of fluid flow along the pathway; and d) at least one hydrophobic portion which defines a path along which the deformable material is guided.
20. A method of manufacturing the assay device (10) of any of claims 1 to 19, including the steps of: a) defining at least one fluid pathway (14a) on a substrate; b) defining at least one reaction chamber (14) on a substrate; c) forming at least one component composed of a deformable material (44) in the device; and d) bonding together at least two substrates to form the device (10).
21. A method of manufacturing the device (10) according to claim 20, wherein the at least one fluid pathway (14a) may be formed by: a) printing, b) etching, c) ablation, d) use of a mould, e) cutting, or a combination of any of steps a) to e).
22. A method of manufacturing the device (10) according to claim 20, wherein the at least one reaction chamber (14) is formed by: a) printing, b) etching, c) ablation, d) use of a mould, e) cutting, or a combination of any of steps a) to e).
23. A method of manufacturing the device (10) according to claim 20, wherein the at least one component (44) composed of a deformable material is formed by: a) printing of the deformable material onto the substrate, b) etching, c) pick-and-placing of components, d) injection of molten material into device using feeder tubes, or a combination of steps a) to d).
24. A method of manufacturing the device (10) according to claim 20, wherein the at least one substrate is bonded by: a) adhesives, b) curing, c) mechanical fixing, d) heating, e) anodic bonding, or a combination of steps a) to e).
25. Apparatus for varying the rate of fluid flow along a pathway (75), the apparatus including at least one pathway (75) and a volume of deformable material (78) disposed within the pathway whereby, in use, a change of state of the deformable material causes a change of the rate of fluid flow along the pathway.

26. Apparatus for varying the rate of fluid flow along a pathway (75), the apparatus including at least one pathway (75) and a volume of deformable material (78) disposed adjacent the pathway whereby, in use, a change of state of the deformable material causes a change of the rate of fluid flow along the pathway.
27. Apparatus according to claim 25 or 26 further including at least one chamber in fluid connection with the pathway.
28. Apparatus according to claim 27 wherein a volume of deformable material is disposed within the chamber.
29. Apparatus according to any of claims 25 to 28 wherein at least one recess (72) capable of receiving deformable material is located substantially adjacent the pathway (75).
30. Apparatus according to claim 29 wherein the at least one recess (72) has an opening (74) which acts as a vent in order to permit the flow of gas therethrough.
31. Apparatus according to any of claims 25 to 30 including at least one hydrophobic region (76) in order to guide fluid along a predetermined path.
32. Apparatus according to any of claims 25 to 31 including means for the supply and/or removal of heat from the apparatus in order to increase or decrease the rate of change of state of the deformable material.
33. Apparatus according to any of claims 25 to 32 including means for the supply of (i) pressure, (ii) uv radiation, (iii) light, (iv) ultrasonic energy or a combination of any of (i) to (iv) to the apparatus in order to change the state of the deformable material.
34. Apparatus according to any of claims 25 to 33 wherein the deformable material (78) includes a polymer.
35. Apparatus according to any of claims 25 to 33 wherein the deformable material (78) includes polypropylene polystyrene.
36. Apparatus according to any of claims 25 to 30 including at least one hydrophobic portion (76) which defines a path along which deformable material is guided.

37. Apparatus for varying the rate of fluid flow along a pathway (75), the apparatus including:
a) at least one pathway (75); b) a volume of deformable material (78) disposed within the pathway, which, in use, changes its state so as to cause a change of the rate of fluid flow along the pathway; and c) at least one hydrophobic region (76) which defines a path along which deformable material is guided.
38. Apparatus for varying the rate of fluid flow along a pathway (75), the apparatus including:
a) at least one pathway (75); b) a volume of deformable material (78) disposed adjacent the pathway, which, in use, change its state so as to cause a change of the rate of fluid flow along a pathway; and c) at least one hydrophobic region (76) which defines a path along which deformable material is guided.
39. A method of varying the rate of fluid flow along a pathway (75) comprising the steps of: providing at least one recess (72) located substantially adjacent the pathway (75); locating a plug of deformable material (78) in the pathway so that the material substantially restricts the flow of fluid in the pathway; and changing the state of the deformable material so that at least a portion of the material passes into the at least one recess thereby permitting flow of the fluid along the pathway.
40. A method of varying the rate of fluid flow along a pathway comprising the steps of: providing at least one recess (72) located substantially adjacent the pathway (75); locating a volume of deformable material (78) in the at least one recess; and changing the state of the deformable material so that at least a portion of the material passes into the pathway thereby substantially restricting flow of the fluid along the pathway.
41. A method of varying the rate of fluid flow along a pathway (75) comprising the steps of: providing a pathway (75); locating a volume of deformable material (78) in the pathway so that it substantially restricts the flow of fluid along the pathway (75); and changing the state of the deformable material so that at least a portion of the material (78) passes along a predetermined path thereby permitting flow of the fluid along the pathway.
42. A method of varying the rate of fluid flow along a pathway (75) comprising the steps of: providing a pathway (75); locating a volume of deformable material (78) in the pathway so that it substantially permits the flow of fluid along the pathway; and changing the state of the deformable material so that at least a portion of the material (78) passes along a predetermined path thereby substantially restricting flow of the fluid along the pathway.

43. A method according to claim 41 or claim 42 wherein the predetermined path is defined by one or more hydrophobic regions (76).
44. A method according to claims 39 to 42 whereby the state of the deformable material (78) is changed by applying to said material (i) heat, (ii) pressure, (iii) uv radiation, (iv) light, (v) ultrasonic energy or a combination of any of (i) to (v).
45. A method of varying the rate of fluid flow along a pathway (75) comprising the steps of: providing at least one recess (72) located substantially adjacent the pathway (75); locating a plug of deformable material (78) in the pathway so that the material substantially restricts fluid flow in the pathway; and changing the state of the deformable material so that at least a portion of the material passes along a predetermined path into the at least one recess thereby permitting flow of the fluid along the pathway, wherein the predetermined path is defined by one more hydrophobic regions.
46. A method of varying the rate of fluid flow along a pathway comprising the steps of: providing at least one recess (72) located substantially adjacent the pathway (75); locating a volume of deformable material (78) in the at least one recess; and changing the state of the deformable material so that at least a portion of the material passes along a predetermined path into the pathway thereby substantially restricting flow of the fluid along the pathway, wherein the predetermined path is defined by one or more hydrophobic regions.
47. A method of varying the rate of fluid flow along a pathway (75) comprising the steps of: providing a pathway (75); locating a volume of deformable material (78) in the pathway so that it substantially restricts fluid flow along the pathway (75); and changing the state of the deformable material so that at least a portion of the material (78) passes along a predetermined path thereby permitting flow of the fluid along the pathway, wherein the predetermined path is defined by one or more hydrophobic regions.
48. A method of varying the rate of fluid flow along a first pathway (75) comprising the steps of: providing a first pathway (75); locating a volume of deformable material (78) in the first pathway; flowing a fluid along the first pathway past the material; and changing the state of the material so that at least a portion of the material (78) passes along a second pathway so as to restrict fluid flow along the first pathway, said second pathway being defined by one or more hydrophobic regions.

Fig.1.





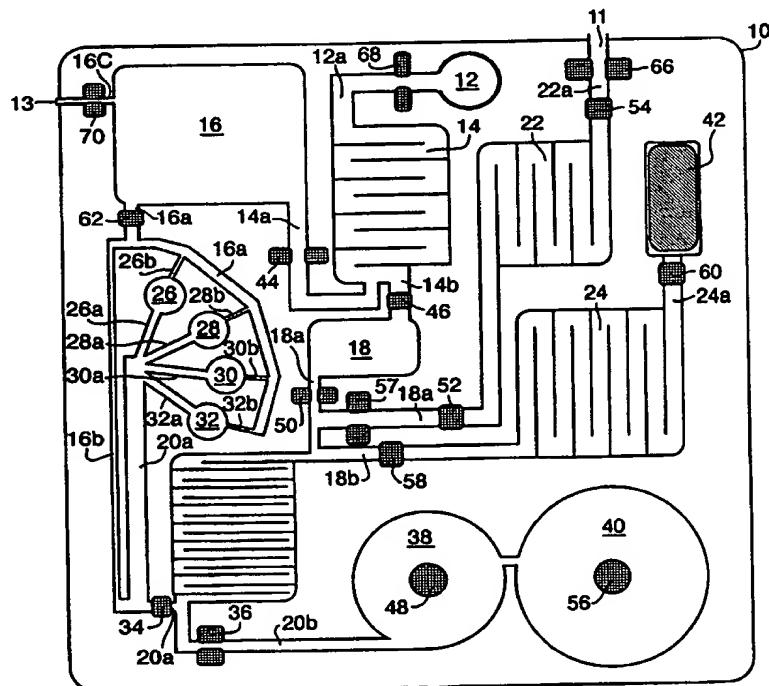
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(54) Title: APPARATUS FOR, AND METHOD OF, VARYING THE RATE OF FLOW OF FLUID ALONG A PATHWAY

(57) Abstract

An apparatus for varying the rate of flow of a fluid in a pathway by the use of deformable valves and clamps which change their size, position, state or function on application of heat and/or pressure is described. A disposable chemical assay device (10), and a method of using the device incorporating the apparatus are also described. The assay device (10) includes an inlet port (12), a reaction chamber (14), a waste depot (16), a filter chamber (18), a processing chamber (20), wash solution/reagent reservoirs (22 and 24), an array of metered readout cells (26, 28, 30, and 32), and breather tubes (11 and 13). The invention, in a preferred embodiment, offers an advantage over existing assay devices because the condition or state of the deformable valves and clamps may be changed. Therefore more complex operations and procedures may be performed by the assay device (10) than has been previously achievable.



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APPARATUS FOR, AND METHOD OF, VARYING THE RATE OF FLOW OF FLUID ALONG A PATHWAY

5 Technical Field

This invention relates to an apparatus for and method of varying the rate of flow of a fluid along a pathway. More particularly, but not exclusively, the invention varies the rate of flow of fluid along a pathway in a wet chemistry analysis system.

10 Background Art

A common feature of all "wet chemistry" analysis or assay systems is that analyte, together with one or more reagents, usually passes through a series of processes or procedures. These include: mixing, reacting, incubating, filtering, decanting, metering and dividing. In short, some form of fluid handling is a common and important feature of most assay

15 systems.

International Patent Application WO-A1-9419484 (Biocircuits Corporation) describes a disposable device for use in diagnostic assays and comprises a number of chambers and interconnecting pathways. Capillary valves are used to enhance control over fluid flow in the device. One type of capillary valve comprises a fluid flow capillary channel and a control capillary channel which intersect each other at right angles. The intersection disrupts fluid flow in the flow capillary channel when the control capillary is empty, but does not impede flow through the flow capillary channel when it is full. Thus, fluid flow through the device can be controlled by either filling or emptying the control capillary with liquid.

A similar disposable device is described in International Patent Application WO-A1-9727324 (David Sarnoff Research Center). This device uses valves and pumps for controlling the flow of fluid. The valves used may be of the plunger type such that the 30 valve has a piston and plunger rod. The diameter of the plunger rods is typically of the order of 60 μ m and the piston diameter is typically of the order of 200 μ m.

In US Patent No. 5,278,079 (Enzymatics Inc.) a diagnostic device having capillary tubes is described. The capillary tubes contain a volume of water-expandable polymer which forms

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a seal in the tubes when it is in contact with an aqueous medium. However, once sealed, the capillary tubes cannot be easily reopened.

5 In conventional analysis techniques, fluid handling relies on precisely engineered fluid controllers such as valves, taps and fluid delivery systems. These fluid controllers are expensive and difficult to manufacture. They are therefore not appropriate for inclusion in disposable units due to their number and cost.

10 An aim of the present invention is to overcome the aforementioned problems by providing a means for varying the flow of fluid along a pathway.

Disclosure of Invention

15 According to a first embodiment of the invention there is provided a method of varying the rate of fluid flow along a pathway comprising the steps of: providing at least one recess located substantially adjacent the pathway; locating a plug of deformable material in the pathway so that the material substantially restricts the flow of fluid in the pathway; and changing the state of the deformable material so that at least a portion of the material passes into the at least one recess thereby permitting flow of the fluid along the pathway.

20 According to a second embodiment of the invention there is provided method of varying the rate of fluid flow along a pathway comprising the steps of: providing at least one recess located substantially adjacent the pathway; locating a volume of deformable material in the at least one recess; and changing the state of the deformable material so that at least a portion of the material passes into the pathway thereby substantially restricting flow of the fluid along the pathway.

25 According to a third embodiment of the invention there is provided a method of varying the rate of fluid flow along a pathway comprising the steps of: providing a pathway; locating a volume of deformable material in the pathway so that it substantially restricts the flow of fluid along the pathway; and changing the state of the deformable material so that at least a portion of the material passes along a predetermined path thereby permitting flow of the fluid along the pathway.

According to a fourth embodiment of the invention there is provided a method of varying the rate of fluid flow along a pathway comprising the steps of: providing a pathway; locating a volume of deformable material in the pathway so that it substantially permits the flow of fluid along the pathway; and changing the state of the deformable material so that at least a portion of the material passes along a predetermined path thereby substantially restricting flow of the fluid along the pathway.

Preferably the predetermined path is defined by one or more regions that repels or attracts the deformable material. A region having such a property is hereinafter referred to as being hydrophobic.

The state of the deformable material may be changed by applying to the deformable material (i) heat, (ii) pressure, (iii) uv radiation, (iv) light, (v) ultrasonic energy or a combination of any of (i) to (v).

According to a further embodiment of the invention there is provided an apparatus for varying the rate of fluid flow along a pathway, the apparatus including at least one pathway and a volume of deformable material disposed within the pathway whereby, in use, a change of state of the deformable material causes a change of the rate of fluid flow along the pathway.

According to another embodiment of the invention there is provided an apparatus for varying the rate of fluid flow along a pathway, the apparatus including at least one pathway and a volume of deformable material disposed adjacent the pathway whereby, in use, a change of state of the deformable material causes a change of the rate of fluid flow along the pathway.

The apparatus may also include at least one chamber in fluid connection with one or more pathways. A volume of deformable material may be disposed within the at least one chamber.

At least one recess capable of receiving deformable material is preferably located substantially adjacent the at least one pathway. The at least one recess may have an opening which acts as a vent in order to permit the flow of gas therethrough.

- 5 The apparatus may also include at least one hydrophobic region. Thus the flow of material is guided along a predetermined path and discouraged from contacting other regions of the pathway, chamber, or device.

The apparatus may include means for the supply and/or removal of heat from the apparatus
10 in order to increase or decrease the rate of change of state of the deformable material. When heat (or other form of energy) is applied to a region of the apparatus containing the deformable material, the material may change its position, size, state or function. This causes a rate of change in the fluid flow in the pathway. Thus a pathway which is initially obstructed becomes unobstructed, and vice versa.

15 Heater elements may be printed onto the apparatus or a heating tool may be used to apply heat to local areas of the apparatus. Alternatively, heat may be applied to or removed from larger regions of the apparatus, or to a device which includes the apparatus. For example, by dipping into a water bath, heating with an external heater, or by a Peltier.

20 The apparatus may also include means for the supply of pressure, uv radiation, light, ultrasonic energy, or other suitable means for changing the state of the deformable material.

25 The deformable material may be a thermally activated material. Preferably the thermally activated material is wax, contains or is a polymer such as polypropylene polystyrene, a wax/polymer mix, a metal such as Indium, or any other suitable low melting point material that changes its state on application of heat, and on cooling. The terms thermally activated material and wax are hereinafter used interchangeably.

30 In summary, fluid flow along a pathway of the apparatus is varied by way of valves, or clamps, which are preferably formed from a deformable material. The valves and clamps

may be opened and/or closed upon the application of heat, pressure, or other suitable means. The valves and clamps may also be known as gates. Hereinafter, a gate that opens a pathway to the flow of fluid on application of heat is known as a heat openable gate. A gate that closes a pathway to the flow of fluid on application of heat is known as a heat closable gate.

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One example of a heat openable gate has thermally activated material situated in the pathway so as to enable the material in its melted state to flow into at least one recess substantially adjacent the pathway. Air (or other gas) is displaced from the recess by the material and exits through a vent. A type of heat closable gate has thermally activated material situated in at least one recess substantially adjacent the pathway. As the material in its melted state flows from the recess into the pathway, it is replaced by air (or other gas) via the vent.

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15 Alternatively, (or in addition to the material being situated in at least one recess), the material may be situated in the fluid pathway such that the pathway is either substantially or partially obstructed. If the thermally activated material is substantially obstructing the pathway, then the pathway may be opened to the flow of fluid by applying heat to the material. This is a form of heat openable gate. However, if the material is situated so as not to, or only partially, obstruct the flow of fluid, on application of heat the material melts and flows so as substantially obstruct the pathway. This is a form of heat closable gate.

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In a further alternative embodiment, thermally activated material may be arranged to contact at least two points on inner surfaces of the apparatus, forming a clamp. Clamps 25 may be situated in chambers. Upon application of heat to a clamp, the clamp melts, and surfaces of the chambers are separated. Thus a pressure differential is provided to drive fluid along pathways and into, or from, chambers.

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30 Preferably at least one surface contained within the apparatus is resiliently deformable. This is advantageous because it means that if the surfaces are constructed from sufficiently pliable materials, pressure may be applied to a surface, and the surfaces will return to their original state.

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Pathways may contain a volume of material so that upon application of pressure, a rate of change of fluid flow in the pathway occurs. The material may be thermally activated. Thus for a heat closable pathway, a tool may be used to seal the pathway by connecting the upper and lower surfaces with the thermally activated material. Thermally activated material may not be required if the upper and lower surfaces of the pathway may be directly connected to one another. For a heat openable pathway, a tool may make a channel in the wax contained in the pathway. When this occurs the resiliently deformable material of the pathway returns to a previous state. Pathways opened in this way may be resealed by heating and subsequent cooling of the wax.

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Preferably the volumes of deformable material may be accessed independently and sequentially to precisely control the path of fluid flow in the apparatus.

Valves and clamps may be single use structures, or may be reusable.

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The invention may be incorporated into a chemical assay device. The assay device preferably has at least one chamber in fluid connection with at least one pathway, the pathway being adapted to allow fluid to flow to or from said chamber, characterised in that there is provided a volume of deformable material in the pathway whereby, in use, a change of state of the deformable material causes a change of the rate of fluid flow along the pathway.

The deformable material may be situated in the pathway such that the pathway is substantially obstructed or, alternatively, the material may be situated in the pathway such that the pathway is only partially obstructed.

At least one recess may be located substantially adjacent the pathway, the recess being capable of receiving the deformable material.

According to another embodiment of the invention, the assay device preferably has at least one chamber in fluid connection with at least one pathway, the pathway being adapted to allow fluid to flow to or from said chamber, characterised in that there is provided a volume of deformable material situated in a recess, the recess being located substantially

adjacent the pathway whereby, in use, a change of the deformable material causes a change of the rate of fluid flow along the pathway.

An opening may be provided in the recess which acts as a vent.

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The chamber may comprise a deformable envelope and at least two points on the envelope may be connected by way of a volume of deformable material.

A region of the device may have at least one hydrophobic portion so that the flow of the
10 deformable material is guided along a predetermined path.

Preferably the deformable material is thermally deformable. The material may, however,
be mechanically deformable.

15 The device may include heating means for melting the thermally deformable material. The device may also include means for removing heat such as, for example, a heat sink. Heat may selectively be applied and/or removed from individual wax gates and/or clamps.

20 Preferably at least one surface defined by or in the device is resiliently deformable so that the wax gates and/or clamps may be mechanically deformed.

The device may have at least one component from the set of: an inlet port, a reaction chamber, a waste depot, a filter chamber, an infinity capture and processing chamber, a wash solution/reagent reservoir, an array of metered readout cells, and a breather tube.

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The assay device is usually rectangular, but other shapes are equally viable, such as discs or hexagons. Depths of fluid pathways and chambers may be sufficiently narrow to allow filling by capillary action (say 0.02 to 0.2 mm). Pathways may be wider (of the order of a millimeter) where the fluid flow is to be propelled by gravity, a pressure impulse,
30 centrifugal force, or an inertial force. The aforementioned dimensions are consistent with processing fluid samples in the range of approximately 30 to 50 microlitres, and are given by way of example only.

According to a further embodiment of the invention there is provided a method of manufacturing an assay device, the method including the steps of: a) defining at least one fluid pathway on a substrate; b) defining at least one reaction chamber on a substrate; c) forming at least one component composed of a deformable material in the device; and d) bonding together at least two substrates to form the device.

The body of the assay device is preferably formed from a polymer or from a combination of materials including glass, ceramics, or metal. Construction may involve injection moulded components, and/or the joining together of a number of laminae. Pathways and chambers in the assay device may be formed in a plane defined between upper and lower planar sheets. Pathways and chambers may be formed by printing, etching, ablation, cutting of the substrate, moulding of a substrate, or a combination of these. More complex structures may be realised by building up laminae and providing vias for the flow of fluids between adjacent levels.

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Bonding of upper and lower portions of the device is critical for its operation. Bonding can be achieved by means of screen printed adhesives containing for example spacer balls, by cut adhesive gasket materials, by heating sealing, by uv curing, by mechanical fixing, by ultrasonic bonding, or by using a porous-gasket technique, for example as described in US-
20 A-4,865,716.

The assay device may include one or more of the aforementioned gates, valves or clamps. Preferably each individual gate, valve and/or clamp may be accessed independently one from another.

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Wax gates and clamps may also be printed using molten wax or wax dissolved in a solvent, by injection of molten wax into the device using feeder tubes, by etching of the device, or by placing individual wax elements within the apparatus using pick and place equipment.

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Provision may be made for fluid overflow lines, for collection of waste, and for opening and sealing of the device at stages from start of use until disposal.

Brief Description of Figures

Embodiments of the invention will now be described by way of examples, and with reference to the accompanying Figures in which:-

5 Figure 1 is a schematic plan view of a chemical assay device incorporating the invention;

Figure 2a is a plan view of a pathway having an initially open wax gate, where wax is situated in recesses adjacent the pathway;

10 Figure 2b shows a plan view of the pathway of Figure 2a, where the wax gate has been closed upon the application of heat to the gate;

Figure 3a shows a plan view of a pathway having an initially open wax gate, where a volume of wax is situated in the pathway;

15 Figure 3b shows a plan view of the pathway of Figure 3a, where the wax gate has been closed upon the application of heat to the gate;

Figure 4a shows a plan view a pathway having an initially open wax gate, where a volume of wax is situated in the pathway;

20 Figure 4b shows a cross-section of the pathway of Figure 4a;
Figure 4c shows a cross-section of the pathway of Figure 4a, the pathway having been closed on application of heat and pressure;

Figure 5a shows a plan view of a pathway having an initially closed wax gate, where wax is situated in the pathway, and recesses adjacent the pathway;

25 Figure 5b shows a plan view of the pathway of Figure 5a, where the wax gate has been opened upon the application of heat to the gate, wax having flowed into the recesses adjacent the pathway;

Figure 6a shows a plan view of a pathway having an initially closed wax gate, where a volume of wax is situated in the pathway;

30 Figure 6b shows a plan view of the pathway of Figure 6a, where the wax gate has been opened upon the application of heat to the gate;

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Figure 7a shows a cross-section of a pathway having a wax gate which has been closed, and a heating tool;

Figure 7b shows a cross-section of the pathway of Figure 7a, where the pathway has been reopened to the flow of fluid upon application of heat and pressure;

5 Figure 7c shows a plan view of Figure 7b;

Figure 8a shows a plan view of a wax clamp used in a chamber, in which the clamp may be initially closed or open;

Figure 8b shows a cross-section of an deflated chamber having a wax clamp;

10 Figure 8c shows a cross-section of an inflated chamber having a wax clamp;

Figure 9a shows a plan view of a chamber containing a gas generating mixture in fluid connection with a pathway having an initially closed wax gate;

15 Figure 9b shows a plan view of the chamber of Figure 9a having an opened wax gate where fluid has flowed into the chamber (under capillary action or external pressure), and is in contact with the gas producing material contained within the chamber;

Figure 9c shows a plan view of the chamber of Figure 9a where fluid has been driven out of the chamber by a gas; and

Figure 9d shows a cross-section of the chamber and connecting pathway of Figure 9a.

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Detailed Description of Preferred Embodiments

The embodiments of the invention shown in Figures 2 to 9 may be incorporated into the chemical assay device of Figure 1, or they may be included in other types of assay (or other) devices.

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Referring to Figure 1, there is shown a chemical assay device 10 for analysis of blood, or other biological fluid. End products of a reaction or assay may be detected using optical methods. For example, a colour change may be detected by a photo-diode, or a fibre-optic system, or visually. The device has an area typically about 50 cm² and is 3 to 10 millimetres thick. The device 10 may be significantly larger or smaller depending on the complexity of the processes to be carried out and the volumes of fluids to be processed. In this particular embodiment, the assay device 10 is configured to carry out an

immunological assay and this will be described so as to illustrate a method of operation of the invention.

Assay device 10 comprises a generally square, substantially planar substrate in which a number of chambers are interconnected by pathways. Fluid control in the device 10 is by way of wax gates and clamps, which are shown in Figure 1 in their initial (open or closed) states.

The device 10 includes an inlet port 12 in fluid connection with a reaction (e.g., lysing) chamber 14 via a pathway 12a. Chamber 14 leads to waste depot 16 and filter chamber 18 via separate fluid channels 14a and 14b respectively. Filter chamber 18 is in fluid connection with chambers 22 and 24 via respective fluid channels 18a and 18b, and with processing chamber 20. Chamber 22 is initially filled with a wash solution, and chamber 24 is filled with an eluent which is used to displace material from processing chamber 20.

Processing chamber 20 is connected to waste depot 16 via a channel 20a. Channel 20a leads to an array of metered read-out cells 26, 28, 30 and 32. Air from read-out cells 26 to 32 exits into channel 16a. A channel 16b is provided and links channels 20a and 16a. The operation of one of the metered readout cells will now be explained with reference to readout cell 26 of Figure 1.

A region of the analysis area of device 10 comprises a large-bore inlet port 26a leading to a fixed-volume cell 26, which in turn is connected to a narrow-bore outlet tube 26b. Tube 26b leads to pathway 16a, and ultimately to waste depot 16. The structure comprising parts 26a, 26 and 26b has a fluid impedance which is dependent on the amount of fluid therein. Fluid can flow freely into the cell until the narrow-bore section is reached, at which stage the force needed to continue driving the fluid into the cell is greatly increased. At this point the fluid, which flows most readily along the path of least resistance, diverts to the conduit leading to the next cell (28 in this case), and so on. Thus each of the cells 26, 28, 30, 32 is filled in turn, and the volume of fluid entering each cell can be controlled.

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Chamber 20 is also connected to chamber 38 via a fluid pathway 20b, and chamber 38 leads to chamber 40. Chambers 38 and 40 both contain wax clamps. Both chambers 38 and 40 are initially deflated.

- 5 Waste depot 16 connects to breather tube 13 via pathway 16c, and reservoir 22 leads to breather tube 11 via pathway 22a. Breather tubes 11 and 13 ensure that fluid moves freely within the device. Also tubes 11 and 13, when connected to non-critical regions, ensure that any excess fluid does not interfere with any on-going analysis.
- 10 Reservoir 24 is connected to chamber 42 via pathway 24a. Chamber 42 is pre-filled with a dry mixture which, when in contact with a liquid, produces a gas. This is shown diagrammatically in Figure 9.

15 Wax gates are situated in fluid pathways in order to control flow of fluid between the chambers. In Figure 1, gates are shown in their initial states. For example, fluid flow is initially obstructed at gate 34, whereas initially fluid is allowed to flow freely through gate 36.

20 Referring again to Figure 1, a typical sequence of events for an immunological assay is now described. A blood sample (not shown) is injected into the assay device via inlet port 12. Blood fills reaction chamber 14 by capillary action and/or hydrostatic pressure, and excess blood enters the waste depot 16 via pathway 14a. The blood remains in chamber 14 for as long as is required for cell lysing to occur with a reagent. The reagent is introduced into this chamber in a predetermined dose during the manufacture of the device. Heat is 25 then applied to gates 44, 46 and clamp 48 in order to close gate 44, open gate 46, and release clamp 48 thereby actuating partial vacuum chamber 38.

30 The lysed blood is then urged through filter chamber 18 by way of a partial vacuum, and serum fills processing chamber 20. An antigen in the blood serum then bonds to an antibody which has been tagged onto, for example, glass or ceramic beads (not shown). The beads are pre-dosed and introduced in chamber 20 at the manufacturing stage.

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The serum is then washed from the glass beads in chamber 20 by activating heaters at gates 50, 52 and 54, and clamp 56. A partial vacuum in chamber 40 draws wash fluid from chamber 22 through chamber 20 leaving the antigen bound to the particles in chamber 20. Waste wash solution and serum enter chambers 38 and 40.

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The next step is elution. Activating heaters placed at gates 57, 58, 60, 36, 34 and 62 allow the fluid in the reagent reservoir 24 to wet a gas producing powder. Fluid is then driven by the gas through chamber 20 towards analysis cells 26, 28, 30 and 32. As eluent from reservoir 24 passes through chamber 20, antigen is released from the beads and carried in the eluent to the analysis cells. These cells contain reagents such as enzyme systems which react with the antigen, causing either a colour change in the solution, or a change in fluorescence. Any recognised method of optical analysis can then be used for detection and measurement of end products of the reactions. Once cells 26, 28, 30 and 32 are filled, resistance to fluid flow increases in the narrow exit channels 26b, 28b, 30b, and 32b. Excess fluid is then expelled to waste depot 16 through channel 16b.

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Finally, activating heaters at gates 66, 68 and 70 seal the fluids within the device for hygienic disposal.

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Excess fluid is then expelled to waste depot 16 through channel 16b.

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Further embodiments of the invention are described now with reference to Figures 2 to 9 inclusive.

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Figure 2 shows a plan view of a section of a pathway having a wax gate 73 that closes the pathway to the flow of fluid on application of heat. A volume of wax is contained in recess 72. Pathway 75 has a region of hydrophobicity 76 in order to guide the flow of wax. Upon application of heat to gate 73, the wax melts and flows (guided by the hydrophobic region) into the fluid pathway to obstruct the flow of fluid therein. Air enters through inlet 74 and replaces the wax in recess 72. Thus air prevents flowback of the molten wax. As the wax cools, fluid flow along the pathway becomes obstructed.

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In Figure 3 a plan view of a section of pathway having a wax gate 77 is shown. Gate 77 closes pathway 75 to the flow of fluid on application of heat to the gate. A volume of wax 78 is situated in the path of the fluid, only partially obstructing the fluid flow. Upon

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application of heat to the gate, the wax melts and flows to block the pathway guided by the area of hydrophobicity 76. As the wax cools fluid flow along the pathway becomes obstructed.

- 5 Figure 4 shows another form of heat closable pathway. A volume of wax 78 is situated in pathway 75, only partially obstructing the flow of fluid. In order to block the channel, a moveable heat sealing tool 80 is used to apply both pressure and heat, completely sealing the channel. This form of gate requires that at least one sheet forming the pathway is formed from deformable material. If the deformable material can be directly sealed to the
10 second sheet (by heat, pressure or otherwise), then wax is not required.

Figures 5, 6 and 7 all represent forms of heat openable pathways, that is, wax gates that are initially closed to fluid flow in the pathway.

- 15 Figure 5 shows a plan view of a section of a pathway 75 having a gate 79 that opens the pathway to the flow of fluid on application of heat to the gate. A volume of wax is situated in the pathway between two recesses 72. The recess has a region of hydrophobicity 76 in order to guide the flow of wax. Upon application of heat to the gate, the wax melts and flows into the recess. Air exhausts via inlet 74 and is replaced by the wax in the recess, preventing flowback of the molten wax. As the wax cools the fluid pathway opens.
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- Referring to Figure 6, there is shown a plan view of a section of pathway 75 having another form of wax gate 81. The gate opens the pathway to the flow of fluid on application of heat to the gate. A volume of wax 78 is situated in the path of the fluid preventing fluid flow. Upon application of heat to this wax gate, the wax melts and flows in the pathway guided by the area of hydrophobicity 76. As the wax cools, the fluid pathway permits fluid to flow along the pathway.
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- Figure 7 shows another heat openable gate situated in pathway 75. A volume of wax 78 is situated in the pathway, obstructing the flow of fluid. In order to open the pathway to allow the flow of fluid, a moveable heat sealing tool 80 is used to apply both pressure and heat to the pathway. The shape of this heat sealable tool allows the wax to be deformed, forming a channel in the wax. This type of gate requires that at least one sheet forming the pathway is
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deformable and resilient, so that the sheet may return to its original state and leave the pathway open.

In addition to the aforementioned wax valves, components to actuate fluid flow may be required. Capillary action may be used to provide some fluid movement, and this can be extended by opening further fillable or absorbent areas or by opening valves of the types previously described. However, greater flexibility is achieved by employing structures capable of generating pressure differentials, and these are shown in Figures 8 and 9.

- 10 Figure 8 shows a chamber 38 containing a wax clamp 78. Changing the shape and volume of chamber 38 provides a pressure differential to drive (or suck) fluid in the connected pathways and chambers. Two sheets of synthetic plastics material 37a and 37b are fixed together using a volume of wax 78 in order to produce a deflated chamber 38. Upon application of heat, wax clamp 78 melts. This allows the surfaces of chamber 38 to separate thereby inflating the chamber. This results in a pressure change and fluid is sucked through interconnecting pathways. Chamber 38 may be returned to its deflated state by the application of an external pressure (shown in the direction of arrow A) and by heating the wax. As the wax cools, the deformable surfaces are fixed together.
- 15
- 20 Figure 9 shows a further means of generating pressure in order to drive the flow of fluid. Figure 9 shows a chamber 88 connected to a pathway having a closed wax gate 86. The chamber contains a dry gas generating mixture 82, for example sodium bicarbonate with tartaric acid. On applying heat to the wax gate 86, the wax flows to unblock the pathway 85. A solution 84 flows into the chamber 88, wetting the gas generating mixture and causing the generation of a gas. The gas increases the pressure inside the chamber, ejecting the liquid that has flowed into the chamber and propelling it along one or more interconnecting pathways. In addition to the gas generating mixture, an inert absorbent material may be included in the chamber, or the chamber may be filled with capillary matting which acts as a wick.
- 25
- 30 The invention has been described by way of a number of embodiments, and it will be appreciated that variation may be made to these embodiments without departing from the scope of the invention.

Claims

- 5 1. A method of varying the rate of fluid flow along a pathway (75) comprising the steps
of: providing at least one recess (72) located substantially adjacent the pathway (75);
locating a plug of deformable material (78) in the pathway so that the material
substantially restricts the flow of fluid in the pathway; and changing the state of the
deformable material so that at least a portion of the material passes into the at least one
10 recess thereby permitting flow of the fluid along the pathway.
- 15 2. A method of varying the rate of fluid flow along a pathway comprising the steps of:
providing at least one recess (72) located substantially adjacent the pathway (75);
locating a volume of deformable material (78) in the at least one recess; and changing
the state of the deformable material so that at least a portion of the material passes into
the pathway thereby substantially restricting flow of the fluid along the pathway.
- 20 3. A method of varying the rate of fluid flow along a pathway (75) comprising the steps
of: providing a pathway (75); locating a volume of deformable material (78) in the
pathway so that it substantially restricts the flow of fluid along the pathway (75); and
changing the state of the deformable material so that at least a portion of the material
(78) passes along a predetermined path thereby permitting flow of the fluid along the
pathway.
- 25 4. A method of varying the rate of fluid flow along a pathway (75) comprising the steps
of: providing a pathway (75); locating a volume of deformable material (78) in the
pathway so that it substantially permits the flow of fluid along the pathway; and
changing the state of the deformable material so that at least a portion of the material
(78) passes along a predetermined path thereby substantially restricting flow of the fluid
30 along the pathway.
5. A method according to claim 3 or claim 4 wherein the predetermined path is defined by
one or more hydrophobic regions (76).

6. A method according to claims 1 to 5 whereby the state of the deformable material (78) is changed by applying to said material (i) heat, (ii) pressure, (iii) uv radiation, (iv) light, (v) ultrasonic energy or a combination of any of (i) to (v).

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7. Apparatus for varying the rate of fluid flow along a pathway (75), the apparatus including at least one pathway (75) and a volume of deformable material (78) disposed within the pathway whereby, in use, a change of state of the deformable material causes a change of the rate of fluid flow along the pathway.

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8. Apparatus for varying the rate of fluid flow along a pathway (75), the apparatus including at least one pathway (75) and a volume of deformable material (78) disposed adjacent the pathway whereby, in use, a change of state of the deformable material causes a change of the rate of fluid flow along the pathway.

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9. Apparatus according to claim 7 or 8 further including at least one chamber in fluid connection with the pathway.

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10. Apparatus according to claim 9 wherein a volume of deformable material is disposed within the chamber.

11. Apparatus according to any of claims 7 to 10 wherein at least one recess (72) capable of receiving deformable material is located substantially adjacent the pathway (75).

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12. Apparatus according to claim 11 wherein the at least one recess (72) has an opening (74) which acts as a vent in order to permit the flow of gas therethrough.

13. Apparatus according to any of claims 7 to 12 including at least one hydrophobic region (76) in order to guide fluid along a predetermined path.

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14. Apparatus according to any of claims 7 to 13 including means for the supply and/or removal of heat from the apparatus in order to increase or decrease the rate of change of state of the deformable material.

15. Apparatus according to any of claims 7 to 14 including means for the supply of (i) pressure, (ii) uv radiation, (iii) light, (iv) ultrasonic energy or a combination of any of (i) to (iv) to the apparatus in order to change the state of the deformable material.

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16. Apparatus according to any of claims 7 to 15 wherein the deformable material (78) includes a polymer.

17. Apparatus according to any of claims 7 to 15 wherein the deformable material (78)

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includes polypropylene polystyrene.

18. An assay device (10) having at least one chamber (14) in fluid connection with at least one pathway (14a, 14b), the pathway being adapted to allow fluid to flow to/from said chamber (14), characterised in that there is provided a volume of deformable material (46) in the pathway (14b), whereby, in use, a change of state of the deformable material causes a change of the rate of fluid flow along the pathway.

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19. An assay device (10) having at least one chamber (14) in fluid connection with at least one pathway (14a, 14b) the pathway being adapted to allow fluid to flow to/from said chamber (14), characterised in that there is provided a volume of deformable material (44) situated in a recess, the recess being located substantially adjacent the pathway (14a), whereby, in use, a change of state of the deformable material causes a change of the rate of fluid flow along the pathway.

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20. A device (10) according to claim 18 wherein there is at least one recess located substantially adjacent the pathway (14b).

21. A device (10) according to any of claims 18 to 20 wherein an opening is provided, the opening acting as a vent to or from the recess.

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22. A device (10) according to claim 18 wherein the deformable material (46) is situated in the pathway (14b) such that the pathway is partially obstructed.

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23. A device (10) according to any of claims 18 to 22 wherein the chamber (38,40) comprises a deformable envelope and at least two points of the envelope are connected by way of a volume of deformable material (48,56).
- 5 24. A device (10) according to any of claims 18 to 23 wherein a region of the device has at least one hydrophobic portion so that the flow of the deformable material is guided along a predetermined path.
- 10 25. A device (10) according to any of claims 18 to 24 wherein the deformable material is thermally deformable.
26. A device (10) according to any of claims 18 to 24 wherein the deformable material is mechanically deformable.
- 15 27. A device (10) according to any of claims 18 to 26 further including heating means (80).
28. A device (10) according to any of claims 18 to 27 further including a means for removing heat.
- 20 29. A device (10) according to any of claims 18 to 28 wherein the at least one surface defined by or in the device is resiliently deformable.
- 25 30. A device (10) according to any of claims 18 to 29 wherein a plurality of volumes of deformable material are provided, each volume being accessible independently one from another.
- 30 31. A device (10) according to any of claims 18 to 30 having at least one component from the set of: an inlet port (12), a reaction chamber (14), a waste depot (16), a filter chamber (18), an infinity capture and processing chamber (20), a wash solution/reagent reservoir (22), an array of metered readout cells (26,28,30,32), and a breather tube (11, 13).

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32. A device (10) according to any of claims 18 to 31, in which heat is selectively applied to one or more of the volumes of the deformable material.

5 33. A device (10) according to any of claims 18 to 32, in which heat is selectively removed from one or more volumes of the deformable material.

34. A device (10) according to any of claims 18 to 33, in which pressure is selectively applied to at least one region contained within the device.

10 35. A method of manufacturing an assay device (10), including the steps of: a) defining at least one fluid pathway (14a) on a substrate; b) defining at least one reaction chamber (14) on a substrate; c) forming at least one component composed of a deformable material (44) in the device; and d) bonding together at least two substrates to form the device (10).

15 36. A method of manufacturing the device (10) according to claim 35, wherein the at least one fluid pathway (14a) may be formed by: a) printing, b) etching, c) ablation, d) use of a mould, e) cutting, or a combination of any of steps a) to e).

20 37. A method of manufacturing the device (10) according to claim 35, wherein the at least one reaction chamber (14) is formed by: a) printing, b) etching, c) ablation, d) use of a mould, e) cutting, or a combination of any of steps a) to e).

25 38. A method of manufacturing the device (10) according to claim 35, wherein the at least one component (44) composed of a deformable material is formed by: a) printing of the deformable material onto the substrate, b) etching, c) pick-and-placing of components, d) injection of molten material into device using feeder tubes, or a combination of steps a) to d).

30 39. A method of manufacturing the device (10) according to claim 35, wherein the at least one substrate is bonded by: a) adhesives, b) curing, c) mechanical fixing, d) heating, e) anodic bonding, or a combination of steps a) to e).

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40. Apparatus substantially as described herein with reference to Figures 2 to 9.

41. A device (10) substantially as described with reference to Figure 1.

5 42. A method of performing chemical analysis substantially as described with reference to the Figures.

43. A method of varying the rate of fluid flow along a pathway substantially as described herein with reference to the Figures.

AMENDED CLAIMS

[received by the International Bureau on 27 July 1999 (27.07.99);
original claims 1-43 replaced by new claims 1-52 (7 pages)]

1. An assay device (10) having at least one chamber (14) in fluid connection with at least one pathway (14a, 14b), the pathway being adapted to allow fluid to flow to/from said chamber (14), characterised in that there is provided a volume of deformable material (46) in the pathway (14b), which, in use, changes its state so as to cause a change of the rate of fluid flow along the pathway.
2. An assay device (10) having at least one chamber (14) in fluid connection with at least one pathway (14a, 14b) the pathway being adapted to allow fluid to flow to/from said chamber (14), characterised in that there is at least one recess located substantially adjacent the pathway and, situated in the recess, there is provided a volume of deformable material (44) which, in use, changes its state so as to cause a change of the rate of fluid flow along the pathway.
3. An assay device (10) according to claim 1 wherein there is at least one recess located substantially adjacent the pathway (14b).
4. An assay device (10) according to any of claims 1 to 3 wherein an opening is provided, the opening acting as a vent to or from the recess.
5. An assay device (10) according to claim 1 wherein the deformable material (46) is situated in the pathway (14b) such that the pathway is partially obstructed.
6. An assay device (10) according to any of claims 1 to 5 wherein the chamber (38,40) comprises a deformable envelope and at least two points of the envelope are connected by way of a volume of deformable material (48,56).
7. An assay device (10) according to any of claims 1 to 6 wherein a region of the device has at least one hydrophobic portion so that the flow of the deformable material is guided along a predetermined path.
8. An assay device (10) according to any of claims 1 to 7 wherein the deformable material is thermally deformable.
9. An assay device (10) according to any of claims 1 to 7 wherein the deformable material is mechanically deformable.

10. An assay device (10) according to any of claims 1 to 9 further including heating means (80).
11. An assay device (10) according to any of claims 1 to 10 further including a means for removing heat.
12. An assay device (10) according to any of claims 1 to 11 wherein the at least one surface defined by or in the device is resiliently deformable.
13. An assay device (10) according to any of claims 1 to 12 wherein a plurality of volumes of deformable material are provided, each volume being accessible independently one from another.
14. An assay device (10) according to any of claims 1 to 13 having at least one component from the set of: an inlet port (12), a reaction chamber (14), a waste depot (16), a filter chamber (18), an infinity capture and processing chamber (20), a wash solution/reagent reservoir (22), an array of metered readout cells (26,28,30,32), and a breather tube (11, 13).
15. An assay device (10) according to any of claims 1 to 14, in which heat is selectively applied to one or more of the volumes of the deformable material.
16. An assay device (10) according to any of claims 1 to 15, in which heat is selectively removed from one or more volumes of the deformable material.
17. An assay device (10) according to any of claims 1 to 16, in which pressure is selectively applied to at least one region contained within the device.
18. An assay device (10) having: a) at least one chamber (14) in fluid connection with at least one pathway (14a, 14b), the at least one pathway being adapted to allow fluid to flow to/from said at least one chamber (14); b) a volume of deformable material (46) situated in the pathway (14b) which, in use, changes its state so as to cause a change of the rate of fluid flow along the pathway; and c) at least one hydrophobic portion which defines a path along which the deformable material is guided.

19. An assay device (10) having: a) at least one chamber (14) in fluid connection with at least one pathway (14a, 14b), the at least one pathway being adapted to allow fluid to flow to/from said at least one chamber (14); b) at least one recess located substantially adjacent the pathway; c) a volume of deformable material (44) situated in the recess which, in use, changes its state so as to cause a change of the rate of fluid flow along the pathway; and d) at least one hydrophobic portion which defines a path along which the deformable material is guided.
20. A method of manufacturing the assay device (10) of any of claims 1 to 19, including the steps of: a) defining at least one fluid pathway (14a) on a substrate; b) defining at least one reaction chamber (14) on a substrate; c) forming at least one component composed of a deformable material (44) in the device; and d) bonding together at least two substrates to form the device (10).
21. A method of manufacturing the device (10) according to claim 20, wherein the at least one fluid pathway (14a) may be formed by: a) printing, b) etching, c) ablation, d) use of a mould, e) cutting, or a combination of any of steps a) to e).
22. A method of manufacturing the device (10) according to claim 20, wherein the at least one reaction chamber (14) is formed by: a) printing, b) etching, c) ablation, d) use of a mould, e) cutting, or a combination of any of steps a) to e).
23. A method of manufacturing the device (10) according to claim 20, wherein the at least one component (44) composed of a deformable material is formed by: a) printing of the deformable material onto the substrate, b) etching, c) pick-and-placing of components, d) injection of molten material into device using feeder tubes, or a combination of steps a) to d).
24. A method of manufacturing the device (10) according to claim 20, wherein the at least one substrate is bonded by: a) adhesives, b) curing, c) mechanical fixing, d) heating, e) anodic bonding, or a combination of steps a) to e).
25. Apparatus for varying the rate of fluid flow along a pathway (75), the apparatus including at least one pathway (75) and a volume of deformable material (78) disposed within the pathway whereby, in use, a change of state of the deformable material causes a change of the rate of fluid flow along the pathway.

26. Apparatus for varying the rate of fluid flow along a pathway (75), the apparatus including at least one pathway (75) and a volume of deformable material (78) disposed adjacent the pathway whereby, in use, a change of state of the deformable material causes a change of the rate of fluid flow along the pathway.
27. Apparatus according to claim 25 or 26 further including at least one chamber in fluid connection with the pathway.
28. Apparatus according to claim 27 wherein a volume of deformable material is disposed within the chamber.
29. Apparatus according to any of claims 25 to 28 wherein at least one recess (72) capable of receiving deformable material is located substantially adjacent the pathway (75).
30. Apparatus according to claim 29 wherein the at least one recess (72) has an opening (74) which acts as a vent in order to permit the flow of gas therethrough.
31. Apparatus according to any of claims 25 to 30 including at least one hydrophobic region (76) in order to guide fluid along a predetermined path.
32. Apparatus according to any of claims 25 to 31 including means for the supply and/or removal of heat from the apparatus in order to increase or decrease the rate of change of state of the deformable material.
33. Apparatus according to any of claims 25 to 32 including means for the supply of (i) pressure, (ii) uv radiation, (iii) light, (iv) ultrasonic energy or a combination of any of (i) to (iv) to the apparatus in order to change the state of the deformable material.
34. Apparatus according to any of claims 25 to 33 wherein the deformable material (78) includes a polymer.
35. Apparatus according to any of claims 25 to 33 wherein the deformable material (78) includes polypropylene polystyrene.
36. Apparatus according to any of claims 25 to 30 including at least one hydrophobic portion (76) which defines a path along which deformable material is guided.

37. Apparatus for varying the rate of fluid flow along a pathway (75), the apparatus including:
a) at least one pathway (75); b) a volume of deformable material (78) disposed within the pathway, which, in use, changes its state so as to cause a change of the rate of fluid flow along the pathway; and c) at least one hydrophobic region (76) which defines a path along which deformable material is guided.
38. Apparatus for varying the rate of fluid flow along a pathway (75), the apparatus including:
a) at least one pathway (75); b) a volume of deformable material (78) disposed adjacent the pathway, which, in use, change its state so as to cause a change of the rate of fluid flow along a pathway; and c) at least one hydrophobic region (76) which defines a path along which deformable material is guided.
39. A method of varying the rate of fluid flow along a pathway (75) comprising the steps of: providing at least one recess (72) located substantially adjacent the pathway (75); locating a plug of deformable material (78) in the pathway so that the material substantially restricts the flow of fluid in the pathway; and changing the state of the deformable material so that at least a portion of the material passes into the at least one recess thereby permitting flow of the fluid along the pathway.
40. A method of varying the rate of fluid flow along a pathway comprising the steps of: providing at least one recess (72) located substantially adjacent the pathway (75); locating a volume of deformable material (78) in the at least one recess; and changing the state of the deformable material so that at least a portion of the material passes into the pathway thereby substantially restricting flow of the fluid along the pathway.
41. A method of varying the rate of fluid flow along a pathway (75) comprising the steps of: providing a pathway (75); locating a volume of deformable material (78) in the pathway so that it substantially restricts the flow of fluid along the pathway (75); and changing the state of the deformable material so that at least a portion of the material (78) passes along a predetermined path thereby permitting flow of the fluid along the pathway.
42. A method of varying the rate of fluid flow along a pathway (75) comprising the steps of: providing a pathway (75); locating a volume of deformable material (78) in the pathway so that it substantially permits the flow of fluid along the pathway; and changing the state of the deformable material so that at least a portion of the material (78) passes along a predetermined path thereby substantially restricting flow of the fluid along the pathway.

43. A method according to claim 41 or claim 42 wherein the predetermined path is defined by one or more hydrophobic regions (76).
44. A method according to claims 39 to 42 whereby the state of the deformable material (78) is changed by applying to said material (i) heat, (ii) pressure, (iii) uv radiation, (iv) light, (v) ultrasonic energy or a combination of any of (i) to (v).
45. A method of varying the rate of fluid flow along a pathway (75) comprising the steps of: providing at least one recess (72) located substantially adjacent the pathway (75); locating a plug of deformable material (78) in the pathway so that the material substantially restricts fluid flow in the pathway; and changing the state of the deformable material so that at least a portion of the material passes along a predetermined path into the at least one recess thereby permitting flow of the fluid along the pathway, wherein the predetermined path is defined by one or more hydrophobic regions.
46. A method of varying the rate of fluid flow along a pathway comprising the steps of: providing at least one recess (72) located substantially adjacent the pathway (75); locating a volume of deformable material (78) in the at least one recess; and changing the state of the deformable material so that at least a portion of the material passes along a predetermined path into the pathway thereby substantially restricting flow of the fluid along the pathway, wherein the predetermined path is defined by one or more hydrophobic regions.
47. A method of varying the rate of fluid flow along a pathway (75) comprising the steps of: providing a pathway (75); locating a volume of deformable material (78) in the pathway so that it substantially restricts fluid flow along the pathway (75); and changing the state of the deformable material so that at least a portion of the material (78) passes along a predetermined path thereby permitting flow of the fluid along the pathway, wherein the predetermined path is defined by one or more hydrophobic regions.
48. A method of varying the rate of fluid flow along a first pathway (75) comprising the steps of: providing a first pathway (75); locating a volume of deformable material (78) in the first pathway; flowing a fluid along the first pathway past the material; and changing the state of the material so that at least a portion of the material (78) passes along a second pathway so as to restrict fluid flow along the first pathway, said second pathway being defined by one or more hydrophobic regions.

49. An assay device (10) substantially as described with reference to Figure 1.
50. Apparatus substantially as described herein with reference to Figures 2 to 9.
51. A method of varying the rate of fluid flow along a pathway substantially as described herein with reference to the Figures.
52. A method of performing chemical analysis substantially as described with reference to the Figures.

Fig.1.

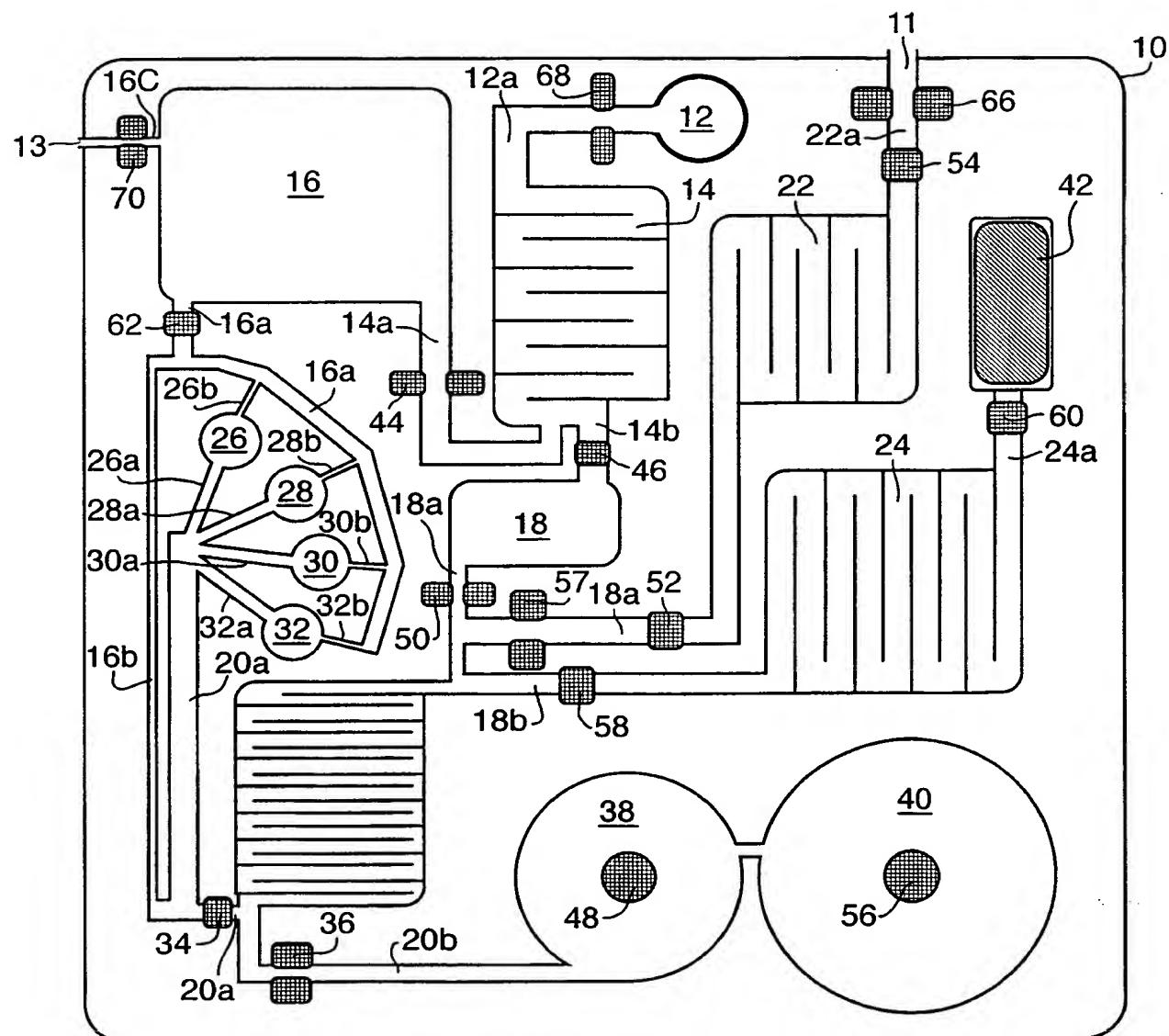


Fig.2a.

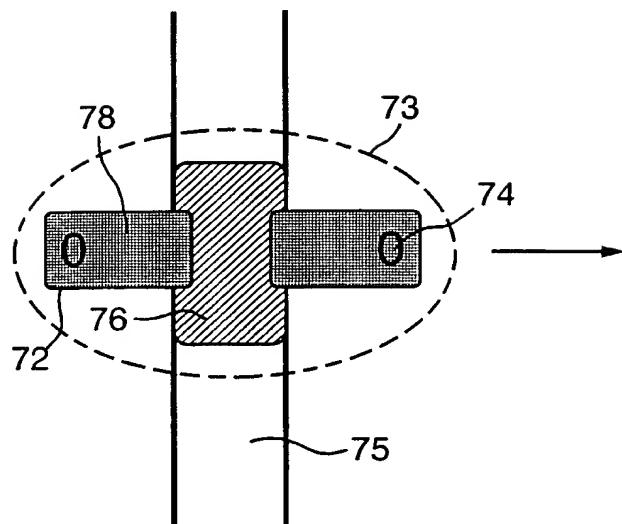


Fig.2b.

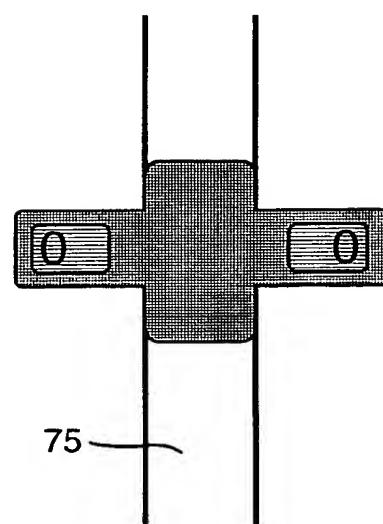


Fig.3a.

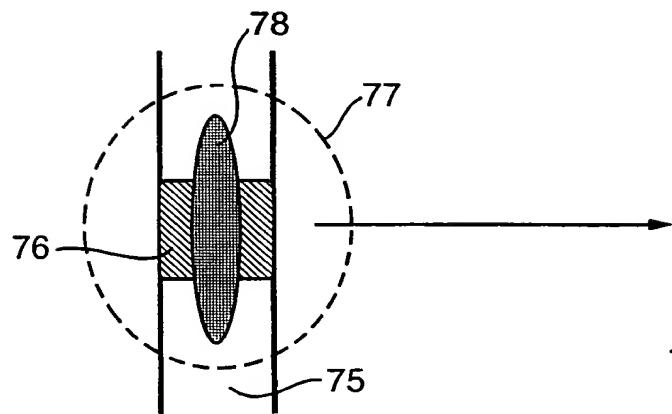


Fig.3b.

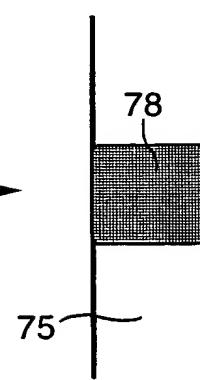


Fig.4a.

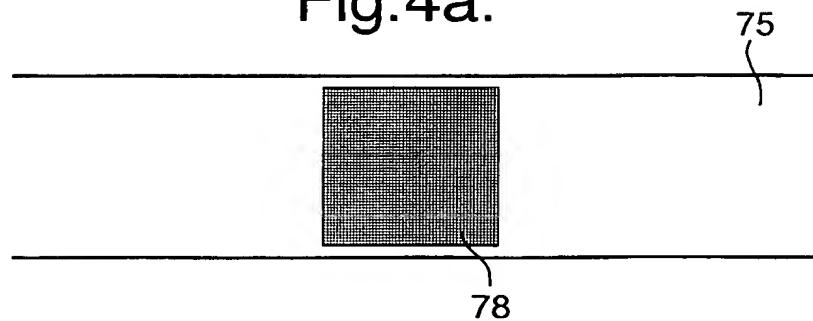


Fig.4b.

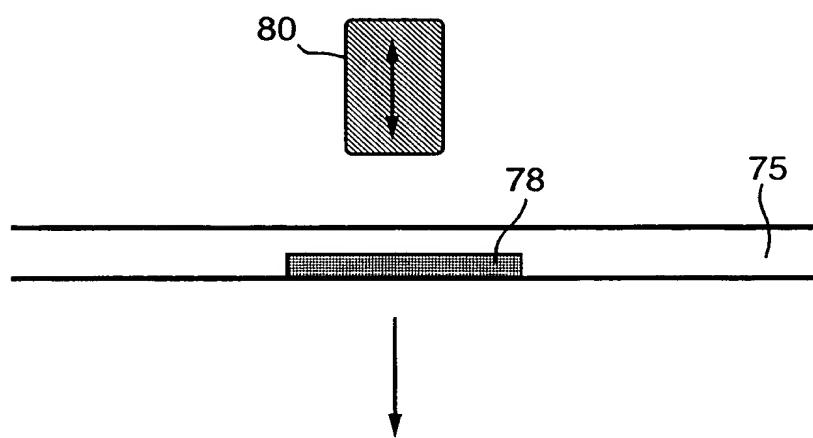


Fig.4c.

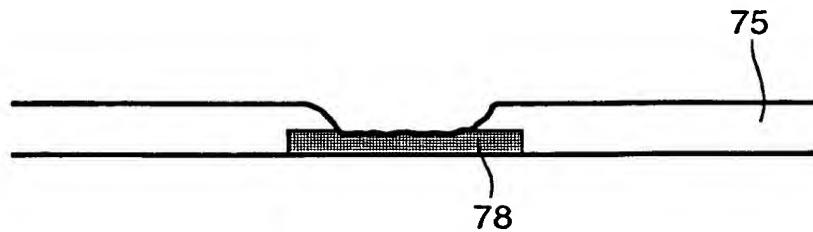


Fig.5a.

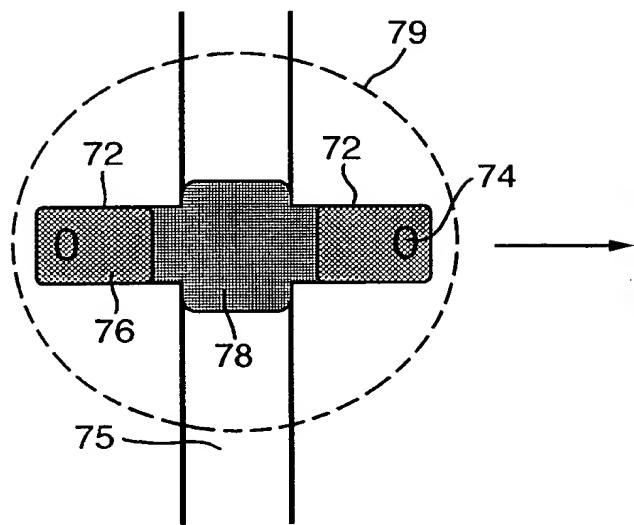


Fig.5b.

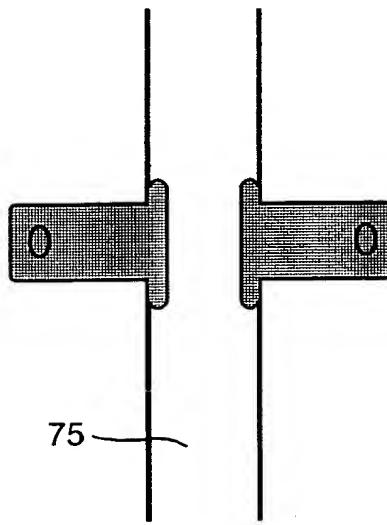


Fig.6a.

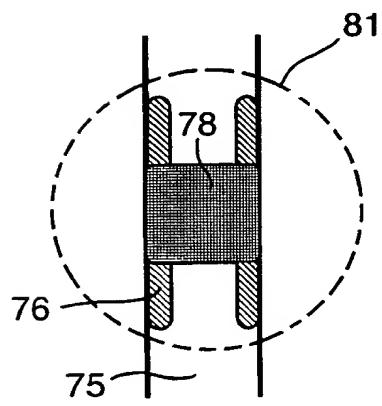
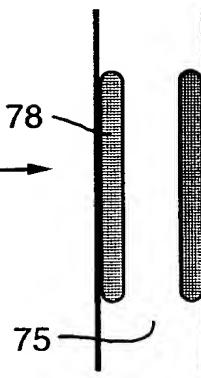
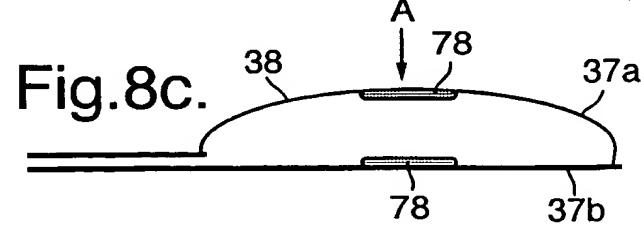
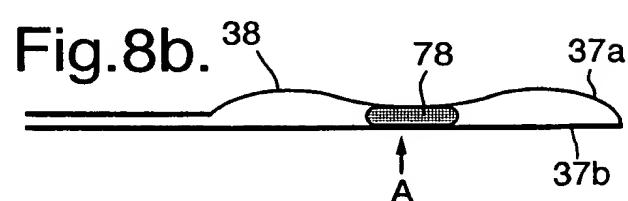
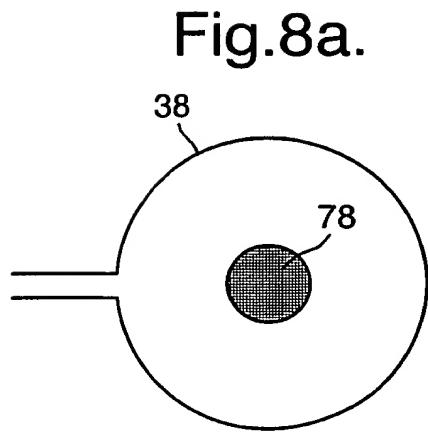
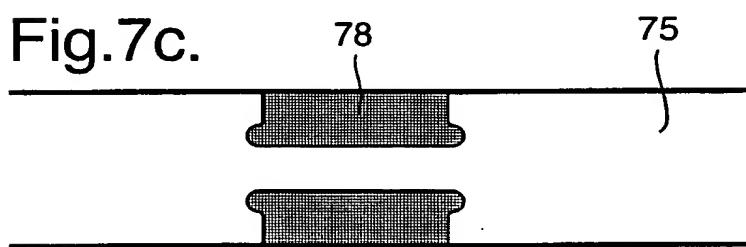
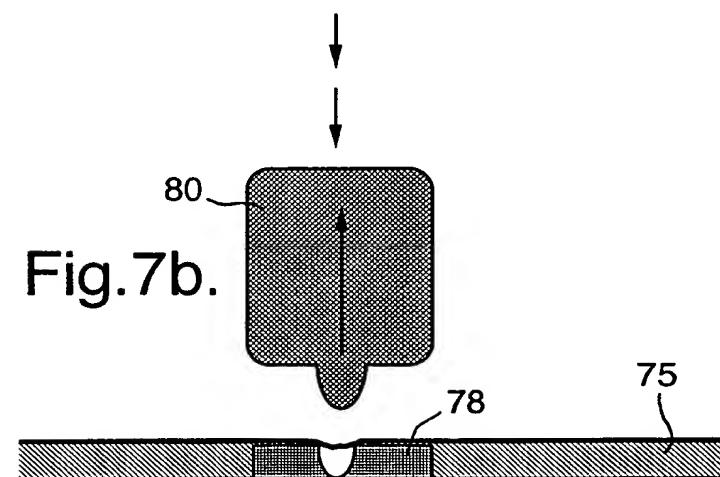
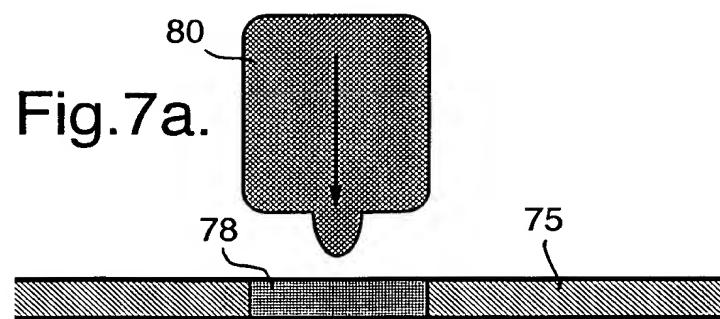


Fig.6b.



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Fig.9a.

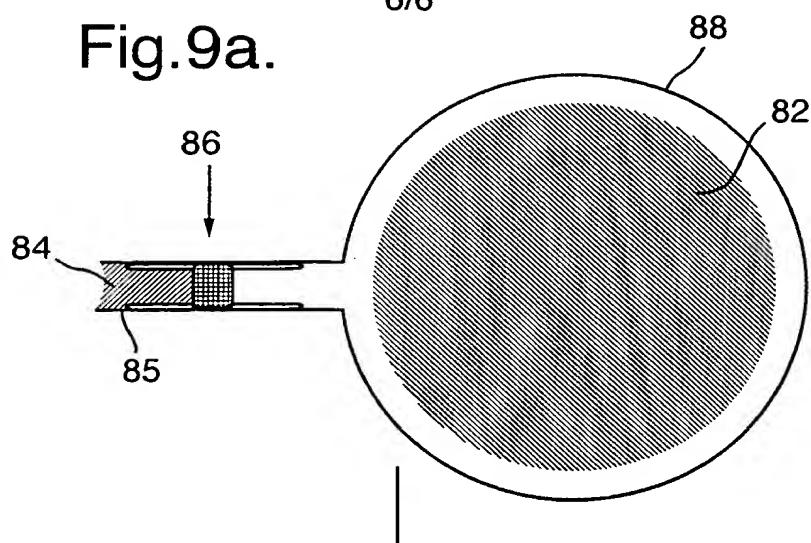


Fig.9b.

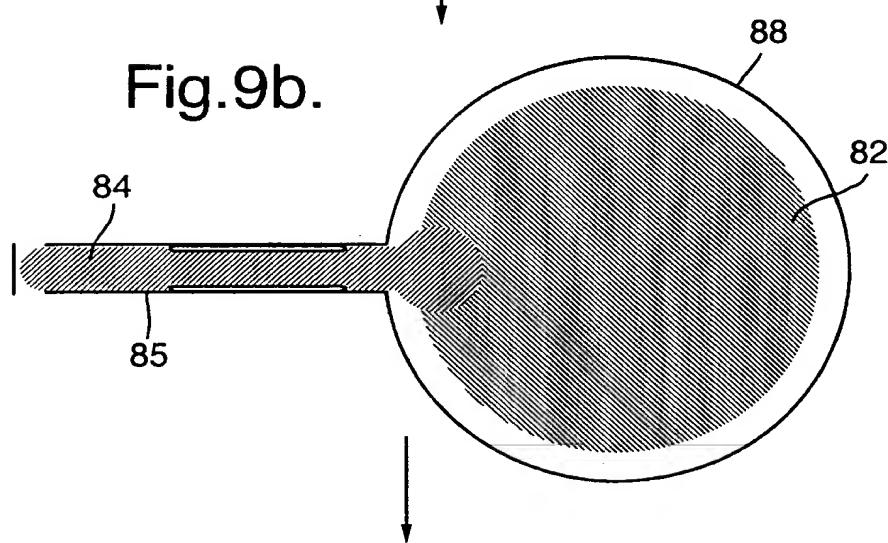


Fig.9c.

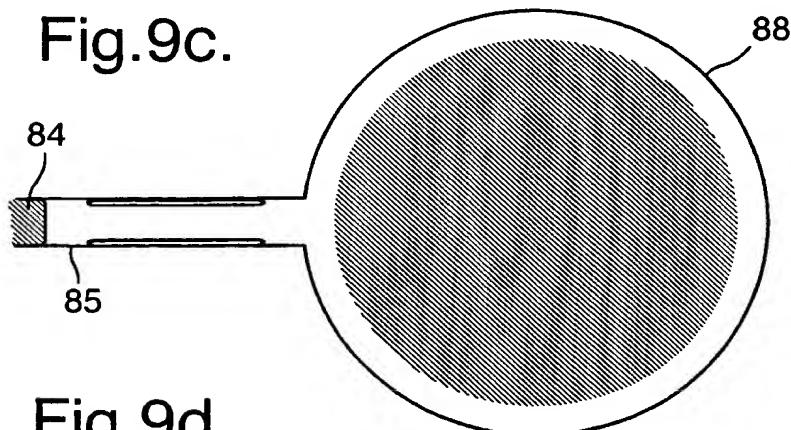
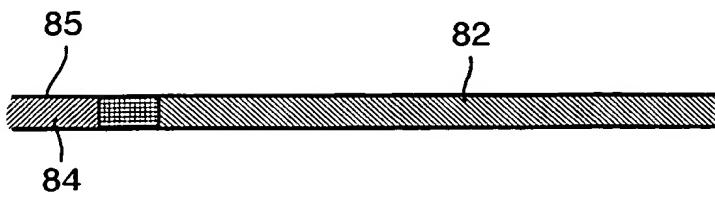


Fig.9d.



INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/00623

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 B01L3/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 B01L F16K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 267 585 A (JONES THOMAS C) 7 December 1993 see abstract; figures 1,2 see column 1, line 38 - column 2, line 19 see column 2, line 65 - column 5, line 3 ---	1-4, 6-8, 11, 15, 16
X	US 4 949 742 A (RANDO JOSEPH F ET AL) 21 August 1990 see abstract; figure 1 see column 1, line 37 - column 2, line 54 see column 3, line 60 - column 4, line 47 ---	1, 2, 6-8, 14
A	---	3-5, 13-19, 25, 27 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

*** Special categories of cited documents :**

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

11 June 1999

Date of mailing of the international search report

21/06/1999

Name and mailing address of the ISA

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Authorized officer

Runser, C

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 278 079 A (GUBINSKI JULIAN ET AL) 11 January 1994 cited in the application see abstract; figures 2-5 see column 2, line 20 - column 3, line 44 see column 4, line 41 - column 5, line 43 see column 6, line 24 - column 7, line 5 see column 8, line 49 - column 9, line 19	4, 7-9, 16, 18, 22, 35
A	---	2, 17, 19, 36-39
X	US 4 549 952 A (COLUMBUS RICHARD L) 29 October 1985 see abstract; figures 1-4 see column 2, line 5 - column 2, line 42 see column 3, line 11 - column 5, line 56	4, 7-9, 16, 18, 22, 35
A	---	2, 19, 31, 36-39
X, P	WO 98 22625 A (BECTON DICKINSON CO ;REGENT OF THE UNIVERSITY OF MI (US)) 28 May 1998 see abstract; figure 1 see page 4, line 23 - page 9, line 17 see page 28, line 24 - page 29, line 2 see page 30, line 3 - page 37, line 21	2, 4, 6-9, 11, 14, 16, 18-20, 25, 27, 32, 35-39
A	-----	1, 3, 28, 31, 33

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 99/00623

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US 5267585	A 07-12-1993	NONE		
US 4949742	A 21-08-1990	NONE		
US 5278079	A 11-01-1994	NONE		
US 4549952	A 29-10-1985	CA 1211157 A DE 3376146 A EP 0110771 A JP 1747373 C JP 4030542 B JP 59105556 A	09-09-1986 05-05-1988 13-06-1984 25-03-1993 22-05-1992 18-06-1984	
WO 9822625	A 28-05-1998	AU 5265698 A		10-06-1998

PATENT COOPERATION TREATY

PCT

REC'D 10 APR 2000

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P.Q. 12,702	FOR FURTHER ACTION		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB99/00623	International filing date (day/month/year) 02/03/1999	Priority date (day/month/year) 02/03/1998	
International Patent Classification (IPC) or national classification and IPC B01L3/00			
<p>Applicant CENTRAL RESEARCH LABORATORIES LIMITED et al.</p>			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 9 sheets, including this cover sheet.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of 10 sheets.</p>			
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input checked="" type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input checked="" type="checkbox"/> Certain observations on the international application 			

Date of submission of the demand 22/09/1999	Date of completion of this report 06.04.00
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Semino, D Telephone No. +49 89 2399 7324



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB99/00623

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

2-15 as originally filed

1,1a as received on 07/03/2000 with letter of 07/03/2000

Claims, No.:

1-52 as received on 07/03/2000 with letter of 07/03/2000

Drawings, sheets:

2/6-6/6 as originally filed

1/6 as received on 07/03/2000 with letter of 07/03/2000

2. The amendments have resulted in the cancellation of:

- the description, pages:
 the claims, Nos.:
 the drawings, sheets:

3. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- the entire international application.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB99/00623

- claims Nos. 49-52.

because:

- the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

- the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 49-52 are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

- the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 2-4,6,7,9,11-13,16-24,28,30,31,35-38,43,45-48
	No:	Claims 1,5,8,10,14,15,25-27,29,32-34,39-42,44
Inventive step (IS)	Yes:	Claims 7,18,19,31,36-38,43,45-48
	No:	Claims 1-6,8-17,20-30,32-35,39-42,44

Industrial applicability (IA)	Yes:	Claims 1-48
	No:	Claims

2. Citations and explanations

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB99/00623

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/00623

Re Item III

**Non-establishment of opinion with regard to novelty, inventive step and
industrial applicability**

1. Claims 49-52 are 'omnibus claims', which are not admissible under Rule 6.2(a) PCT (see also the PCT Guidelines, III-4.10). Reference to the drawings in the claims is permitted only where absolutely necessary; such is not the case here. The claims should be cancelled.
No opinion, therefore, is established with regards to the subject-matter of claims 49-52.

Re Item V

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step
or industrial applicability; citations and explanations supporting such statement**

1. Relevance of the prior art

- 1.1 Document D1 (US-A-5267585) discloses (cf. claim 1, summary of the invention and Figures 1,2) a method and apparatus for controlling the flow in a flow path by means of a deformable elastomeric element, which is contained at least partially within the path and partially in a recess (cf. Figure 1). By application of a force through a control means, the flow can be prevented and, upon release of the force, the flow can be increased (cf. col. 1, l. 64 to col. 2, l. 19).
- 1.2 Document D2 (US-A-4949742) discloses (cf. claims 1,10 and Figure 1) a temperature operated gas valve (and a method for operating it), operable between two volumes (chambers), comprising a conduit between the two volumes and a meltable solid material within a restriction, which, upon heating, allows gas to pass from the first to the second volume and, when the pressure differential between the two volumes becomes small, returns to its initial position by surface tension, where it re-solidify after heating has been discontinued.
- 1.3 Document D3 (US-A-5278079) discloses (cf. claims 1,12,22 and Figures 2,3) a device for sealing a chamber by means of aqueous expandable polymer in a reduced chamber portion which forms a seal in said reduced chamber portion

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/00623

upon contact of the polymer with an aqueous medium, and a method for inhibiting the flow by means of such a device.

- 1.4 Document D4 (US-A-4549952) discloses (cf. claims 1,2 and Figures 1-4) a liquid transport device for transporting two different aqueous liquids within a capillary passage comprising control means on a surface for increasing the viscosity of the liquid flowing past that surface, wherein said control means comprises a water-swellable composition disposed on that surface, whereby the increase in viscosity causes a change in the flow of the liquid. Chambers are provided at the sides of the passage.

2. Conclusions

- 3.1 Before assessing novelty and inventive steps of the subject-matter of the claims over the available art, it is pointed out that many of the claims of the present application are drawn up in such general terms to include embodiments very different from what is detailed in the description and which can be found in very different fields including normal life activities. For example, a rubber tube for delivery of water from a reservoir falls under the definition of claim 1, since the rubber tube itself is of deformable material and upon any pressure in any point of the tube itself the fluid flow behaviour is changed.
- 3.2 In this respect, it is also important to notice that general functional or use terms, such as '**assay**' device in claim 1, do not add any structural peculiarities to the device other than those specified by the physical features of the device itself. This is true also for other terms such as '**reaction**' chamber in claims 14,20,22, insofar as any chamber in use can be used as a reaction chamber, and '**substrate**' in claims 20,23,24, which may refer to any kind of substrate.
- 3.3 In what follows, novelty and inventive steps will be established over the cited prior art. It will be apparent that very different devices in the prior art may fall under the wording of many claims of the present application.
- 4.1 The subject-matter of claims 25,26,29,33,34,39,40,41,42,44 (with regard to pressure) is not novel with respect to D1 (Article 33(2) PCT).

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/00623

- 4.2 The subject-matter of claims 1,5,8,10,15,25,26,27,32,41,42,44 (with regard to heat) is not novel with respect to D2 (Article 33(2) PCT).
- 4.3 The subject-matter of claims 1,5,14 (with regard to inlet port and reaction chamber), 25,27,34,42 is not novel with respect to D3 (Article 33(2) PCT).
- 4.4 The subject-matter of claims 1,5,14 (with regard to inlet port and reaction chamber), 25,27,34,42 is not novel with respect to D4 (Article 33(2) PCT).
- 5.1 The connection of a device as the one in D1 to a chamber does not involve an inventive step (to what else should the skilled man connect such an apparatus?). Therefore the subject-matter of claims 2,3,9,17 does not involve an inventive step (Article 33(3) PCT).
- 5.2 The choice of a particular polymer as in claim 35 appears as just one of many alternative possibilities of material selection. The subject-matter of claim 17 is, therefore, not inventive (Article 33(3) PCT).
- 5.3 A device including a fluid pathway on a substrate, a chamber, one component of deformable material and two substrates bonded together is already disclosed in D3 (cf. Figure 2) and D4 (cf. Figure 2). The method of manufacturing such a device with the common activities listed in claim 20 is, therefore, not inventive either (Article 33(3) PCT).
- 5.4 Also the techniques mentioned in claims 21-24 for forming the different components are common in the field of microfabricated devices. Claims 21-24, therefore, also lack an inventive step (Article 33(3) PCT).
6. There are no examples in the description of changing the state of the deformable material other than by applying heat or pressure. It is not apparent whether or how the skilled man could carry out all the embodiments of claims 33 and 44 (and all dependent thereon) (e.g. by non exemplified UV radiation, light, ultrasonic energy) without undue burden (Article 5 PCT).
7. The additional features in claims 4,6,11,12,13,16,28,30 are not disclosed as such

in the cited prior art. However, it is not apparent from the present application which technical problem they are designed to solve so as to provide the required inventive step (Article 33(3) PCT).

8. The inclusion of a hydrophobic region as in the apparatuses and methods of claims 7,31,43 (and also 18,19,36-38,45-48 see also Item VIII) so as to provide a path along which the deformable material is guided is not disclosed in the prior art, nor it appears to be obvious to the skilled man. The correspondent claims appear, therefore, to involve the required inventive step (Article 33(3) PCT).

Re Item VI

Certain documents cited

1. Document D5 (WO-A-9822625) was filed on 19.11.1997 claiming a priority of 20.11.1996 and published on 28.05.1998. Therefore, it is not part of the prior art (Rule 64(1) PCT); however, it can become part of the state of the art for the examination of novelty at least in the regional phase of the application (e.g. under Article 54(3) EPC).
 - 1.1 Document D5 discloses (cf. p. 9, l. 11-17; p. 32; p. 33; p. 63, chapter IV) devices and methods for sealing of channels with meltable material and the use of such sealed valves to control fluid flow. By application of heat, the meltable material at least partially liquefies and flows over areas of the valve seat and optionally of other auxiliary components (e.g. a diaphragm) so that upon subsequent cooling the valve is sealed. The meltable material may be disposed within a side channel and may be polymer. The valves are used inside microfabricated devices for amplifying nucleic acid target sequences (cf. field of the invention) including various reacting chambers and substrates (see e.g. Figure 1). Hydrophobic regions are used to direct the flow of the treated fluids along the transport channels (cf. e.g. p. 5, last par.; p. 9, l. 18 to p. 10, l. 25).
 - 1.2 The subject-matter of claims 1,2,3,8,10,14,15,25,26,27,29,32,34,40,42,44 (with regard to heat) at least would not be novel with respect to D5 under said Article 54(3) EPC.

Re Item VIII

Certain observations on the international application

1. Claims 1,2 do not satisfy the requirements of Article 6 PCT as far as conciseness is concerned, since they could be made dependent on claims 25,26. Claims 18,19,36-38,45-48 do not satisfy the requirements of Article 6 PCT as far as conciseness is concerned, since they are superfluous with respect to claims 7,31,43(restated as dependent on claims 39-42) respectively.
2. The term 'substantially' used in claims 1,2,3,4,19 has a relative meaning (how much?) and cannot clearly establish the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT).

1

APPARATUS FOR, AND METHOD OF, VARYING THE RATE OF FLOW OF FLUID ALONG A PATHWAY

5 Technical Field

This invention relates to an apparatus for and method of varying the rate of flow of a fluid along a pathway. More particularly, but not exclusively, the invention varies the rate of flow of fluid along a pathway in a wet chemistry analysis system.

10 Background Art

A common feature of all "wet chemistry" analysis or assay systems is that analyte, together with one or more reagents, usually passes through a series of processes or procedures. These include: mixing, reacting, incubating, filtering, decanting, metering and dividing. In short, some form of fluid handling is a common and important feature of most assay 15 systems.

International Patent Application WO-A1-9419484 (Biocircuits Corporation) describes a disposable device for use in diagnostic assays and comprises a number of chambers and interconnecting pathways. Capillary valves are used to enhance control over fluid flow in 20 the device. One type of capillary valve comprises a fluid flow capillary channel and a control capillary channel which intersect each other at right angles. The intersection disrupts fluid flow in the flow capillary channel when the control capillary is empty, but does not impede flow through the flow capillary channel when it is full. Thus, fluid flow through the device can be controlled by either filling or emptying the control capillary with 25 liquid.

A similar disposable device is described in International Patent Application WO-A1-9727324 (David Sarnoff Research Center). This device uses valves and pumps for controlling the flow of fluid. The valves used may be of the plunger type such that the 30 valve has a piston and plunger rod. The diameter of the plunger rods is typically of the order of 60 μm and the piston diameter is typically of the order of 200 μm .

In US Patent No. 5,267,585 (BOC Health Care), a flow control valve is disclosed. A deformable elastomeric element is positioned at least partially within the flow path of a

1a

fluid passing between an inlet and an outlet. By deforming the elastomeric element, the cross-section of the flow path of the fluid is changed, thereby controlling the flow of fluid through the flow control valve.

5 A temperature operated gas valve is described in US Patent No. 4,949,742 (Spectra-
Physics). The valve includes a conduit positioned between high and low pressure gas
regions. Within the conduit is a restriction, and this restriction is closed by a meltable solid
material. When the valve is to be opened, heat is applied to the meltable solid material,
causing some of the material to flow and allow the passage of gas from the higher pressure
10 region to the lower pressure region. When the pressure between the two regions has
substantially equalized, surface tension associated with the restriction in the conduit pulls
the liquified material back into place to close and reseal the valve.

A capillary transport device having an internal capillary transport passage is disclosed in
15 US Patent No. 4,549,952 (Eastman Kodak). To control the liquid flow rate in the passage,
a water-swellable composition (such as gelatin or starch) is used.

International Patent Application WO-A1-9822625 (University of Michigan/Becton
Dickinson) discloses methods and compositions for isothermal amplification of nucleic
20 acids in a micro-fabricated device. The device includes fluid channels connected to an
isothermally regulated reaction chamber. Fluid flow in the channels may be regulated by
the use of meltable materials placed in or alongside the channels.

In US Patent No. 5,278,079 (Enzymatics Inc.) a diagnostic device having capillary tubes is
25 described. The capillary tubes contain a volume of water-expandable polymer which forms

Claims

1. An assay device (10) having at least one chamber (14) in fluid connection with at least one pathway (14a, 14b), the pathway being adapted to allow fluid to flow to/from said chamber (14), characterised in that there is provided a volume of deformable material (46) in the pathway (14b), which, in use, changes its state so as to cause a change of the rate of fluid flow along the pathway.
2. An assay device (10) having at least one chamber (14) in fluid connection with at least one pathway (14a, 14b) the pathway being adapted to allow fluid to flow to/from said chamber (14), characterised in that there is at least one recess located substantially adjacent the pathway and, situated in the recess, there is provided a volume of deformable material (44) which, in use, changes its state so as to cause a change of the rate of fluid flow along the pathway.
3. An assay device (10) according to claim 1 wherein there is at least one recess located substantially adjacent the pathway (14b).
4. An assay device (10) according to any of claims 1 to 3 wherein an opening is provided, the opening acting as a vent to or from the recess.
5. An assay device (10) according to claim 1 wherein the deformable material (46) is situated in the pathway (14b) such that the pathway is partially obstructed.
6. An assay device (10) according to any of claims 1 to 5 wherein the chamber (38,40) comprises a deformable envelope and at least two points of the envelope are connected by way of a volume of deformable material (48,56).
7. An assay device (10) according to any of claims 1 to 6 wherein a region of the device has at least one hydrophobic portion so that the flow of the deformable material is guided along a predetermined path.
8. An assay device (10) according to any of claims 1 to 7 wherein the deformable material is thermally deformable.
9. An assay device (10) according to any of claims 1 to 7 wherein the deformable material is mechanically deformable.

10. An assay device (10) according to any of claims 1 to 9 further including heating means (80).
11. An assay device (10) according to any of claims 1 to 10 further including a means for removing heat.
12. An assay device (10) according to any of claims 1 to 11 wherein the at least one surface defined by or in the device is resiliently deformable.
13. An assay device (10) according to any of claims 1 to 12 wherein a plurality of volumes of deformable material are provided, each volume being accessible independently one from another.
14. An assay device (10) according to any of claims 1 to 13 having at least one component from the set of: an inlet port (12), a reaction chamber (14), a waste depot (16), a filter chamber (18), an infinity capture and processing chamber (20), a wash solution/reagent reservoir (22), an array of metered readout cells (26,28,30,32), and a breather tube (11, 13).
15. An assay device (10) according to any of claims 1 to 14, in which heat is selectively applied to one or more of the volumes of the deformable material.
16. An assay device (10) according to any of claims 1 to 15, in which heat is selectively removed from one or more volumes of the deformable material.
17. An assay device (10) according to any of claims 1 to 16, in which pressure is selectively applied to at least one region contained within the device.
18. An assay device (10) having: a) at least one chamber (14) in fluid connection with at least one pathway (14a, 14b), the at least one pathway being adapted to allow fluid to flow to/from said at least one chamber (14); b) a volume of deformable material (46) situated in the pathway (14b) which, in use, changes its state so as to cause a change of the rate of fluid flow along the pathway; and c) at least one hydrophobic portion which defines a path along which the deformable material is guided.

19. An assay device (10) having: a) at least one chamber (14) in fluid connection with at least one pathway (14a, 14b), the at least one pathway being adapted to allow fluid to flow to/from said at least one chamber (14); b) at least one recess located substantially adjacent the pathway; c) a volume of deformable material (44) situated in the recess which, in use, changes its state so as to cause a change of the rate of fluid flow along the pathway; and d) at least one hydrophobic portion which defines a path along which the deformable material is guided.
20. A method of manufacturing the assay device (10) of any of claims 1 to 19, including the steps of: a) defining at least one fluid pathway (14a) on a substrate; b) defining at least one reaction chamber (14) on a substrate; c) forming at least one component composed of a deformable material (44) in the device; and d) bonding together at least two substrates to form the device (10).
21. A method of manufacturing the device (10) according to claim 20, wherein the at least one fluid pathway (14a) may be formed by: a) printing, b) etching, c) ablation, d) use of a mould, e) cutting, or a combination of any of steps a) to e).
22. A method of manufacturing the device (10) according to claim 20, wherein the at least one reaction chamber (14) is formed by: a) printing, b) etching, c) ablation, d) use of a mould, e) cutting, or a combination of any of steps a) to e).
23. A method of manufacturing the device (10) according to claim 20, wherein the at least one component (44) composed of a deformable material is formed by: a) printing of the deformable material onto the substrate, b) etching, c) pick-and-placing of components, d) injection of molten material into device using feeder tubes, or a combination of steps a) to d).
24. A method of manufacturing the device (10) according to claim 20, wherein the at least one substrate is bonded by: a) adhesives, b) curing, c) mechanical fixing, d) heating, e) anodic bonding, or a combination of steps a) to e).
25. Apparatus for varying the rate of fluid flow along a pathway (75), the apparatus including at least one pathway (75) and a volume of deformable material (78) disposed within the pathway whereby, in use, a change of state of the deformable material causes a change of the rate of fluid flow along the pathway.

26. Apparatus for varying the rate of fluid flow along a pathway (75), the apparatus including at least one pathway (75) and a volume of deformable material (78) disposed adjacent the pathway whereby, in use, a change of state of the deformable material causes a change of the rate of fluid flow along the pathway.
27. Apparatus according to claim 25 or 26 further including at least one chamber in fluid connection with the pathway.
28. Apparatus according to claim 27 wherein a volume of deformable material is disposed within the chamber.
29. Apparatus according to any of claims 25 to 28 wherein at least one recess (72) capable of receiving deformable material is located substantially adjacent the pathway (75).
30. Apparatus according to claim 29 wherein the at least one recess (72) has an opening (74) which acts as a vent in order to permit the flow of gas therethrough.
31. Apparatus according to any of claims 25 to 30 including at least one hydrophobic region (76) in order to guide fluid along a predetermined path.
32. Apparatus according to any of claims 25 to 31 including means for the supply and/or removal of heat from the apparatus in order to increase or decrease the rate of change of state of the deformable material.
33. Apparatus according to any of claims 25 to 32 including means for the supply of (i) pressure, (ii) uv radiation, (iii) light, (iv) ultrasonic energy or a combination of any of (i) to (iv) to the apparatus in order to change the state of the deformable material.
34. Apparatus according to any of claims 25 to 33 wherein the deformable material (78) includes a polymer.
35. Apparatus according to any of claims 25 to 33 wherein the deformable material (78) includes polypropylene polystyrene.
36. Apparatus according to any of claims 25 to 30 including at least one hydrophobic portion (76) which defines a path along which deformable material is guided.

37. Apparatus for varying the rate of fluid flow along a pathway (75), the apparatus including:
a) at least one pathway (75); b) a volume of deformable material (78) disposed within the pathway, which, in use, changes its state so as to cause a change of the rate of fluid flow along the pathway; and c) at least one hydrophobic region (76) which defines a path along which deformable material is guided.
38. Apparatus for varying the rate of fluid flow along a pathway (75), the apparatus including:
a) at least one pathway (75); b) a volume of deformable material (78) disposed adjacent the pathway, which, in use, change its state so as to cause a change of the rate of fluid flow along a pathway; and c) at least one hydrophobic region (76) which defines a path along which deformable material is guided.
39. A method of varying the rate of fluid flow along a pathway (75) comprising the steps of: providing at least one recess (72) located substantially adjacent the pathway (75); locating a plug of deformable material (78) in the pathway so that the material substantially restricts the flow of fluid in the pathway; and changing the state of the deformable material so that at least a portion of the material passes into the at least one recess thereby permitting flow of the fluid along the pathway.
40. A method of varying the rate of fluid flow along a pathway comprising the steps of: providing at least one recess (72) located substantially adjacent the pathway (75); locating a volume of deformable material (78) in the at least one recess; and changing the state of the deformable material so that at least a portion of the material passes into the pathway thereby substantially restricting flow of the fluid along the pathway.
41. A method of varying the rate of fluid flow along a pathway (75) comprising the steps of: providing a pathway (75); locating a volume of deformable material (78) in the pathway so that it substantially restricts the flow of fluid along the pathway (75); and changing the state of the deformable material so that at least a portion of the material (78) passes along a predetermined path thereby permitting flow of the fluid along the pathway.
42. A method of varying the rate of fluid flow along a pathway (75) comprising the steps of: providing a pathway (75); locating a volume of deformable material (78) in the pathway so that it substantially permits the flow of fluid along the pathway; and changing the state of the deformable material so that at least a portion of the material (78) passes along a predetermined path thereby substantially restricting flow of the fluid along the pathway.

43. A method according to claim 41 or claim 42 wherein the predetermined path is defined by one or more hydrophobic regions (76).
44. A method according to claims 39 to 42 whereby the state of the deformable material (78) is changed by applying to said material (i) heat, (ii) pressure, (iii) uv radiation, (iv) light, (v) ultrasonic energy or a combination of (i) to (v).
45. A method of varying the rate of fluid flow along a pathway (75) comprising the steps of: providing at least one recess (72) located substantially adjacent the pathway (75); locating a plug of deformable material (78) in the pathway so that the material substantially restricts fluid flow in the pathway; and changing the state of the deformable material so that at least a portion of the material passes along a predetermined path into the at least one recess thereby permitting flow of the fluid along the pathway, wherein the predetermined path is defined by one more hydrophobic regions.
46. A method of varying the rate of fluid flow along a pathway comprising the steps of: providing at least one recess (72) located substantially adjacent the pathway (75); locating a volume of deformable material (78) in the at least one recess; and changing the state of the deformable material so that at least a portion of the material passes along a predetermined path into the pathway thereby substantially restricting flow of the fluid along the pathway, wherein the predetermined path is defined by one or more hydrophobic regions.
47. A method of varying the rate of fluid flow along a pathway (75) comprising the steps of: providing a pathway (75); locating a volume of deformable material (78) in the pathway so that it substantially restricts fluid flow along the pathway (75); and changing the state of the deformable material so that at least a portion of the material (78) passes along a predetermined path thereby permitting flow of the fluid along the pathway, wherein the predetermined path is defined by one or more hydrophobic regions.
48. A method of varying the rate of fluid flow along a first pathway (75) comprising the steps of: providing a first pathway (75); locating a volume of deformable material (78) in the first pathway; flowing a fluid along the first pathway past the material; and changing the state of the material so that at least a portion of the material (78) passes along a second pathway so as to restrict fluid flow along the first pathway, said second pathway being defined by one or more hydrophobic regions.

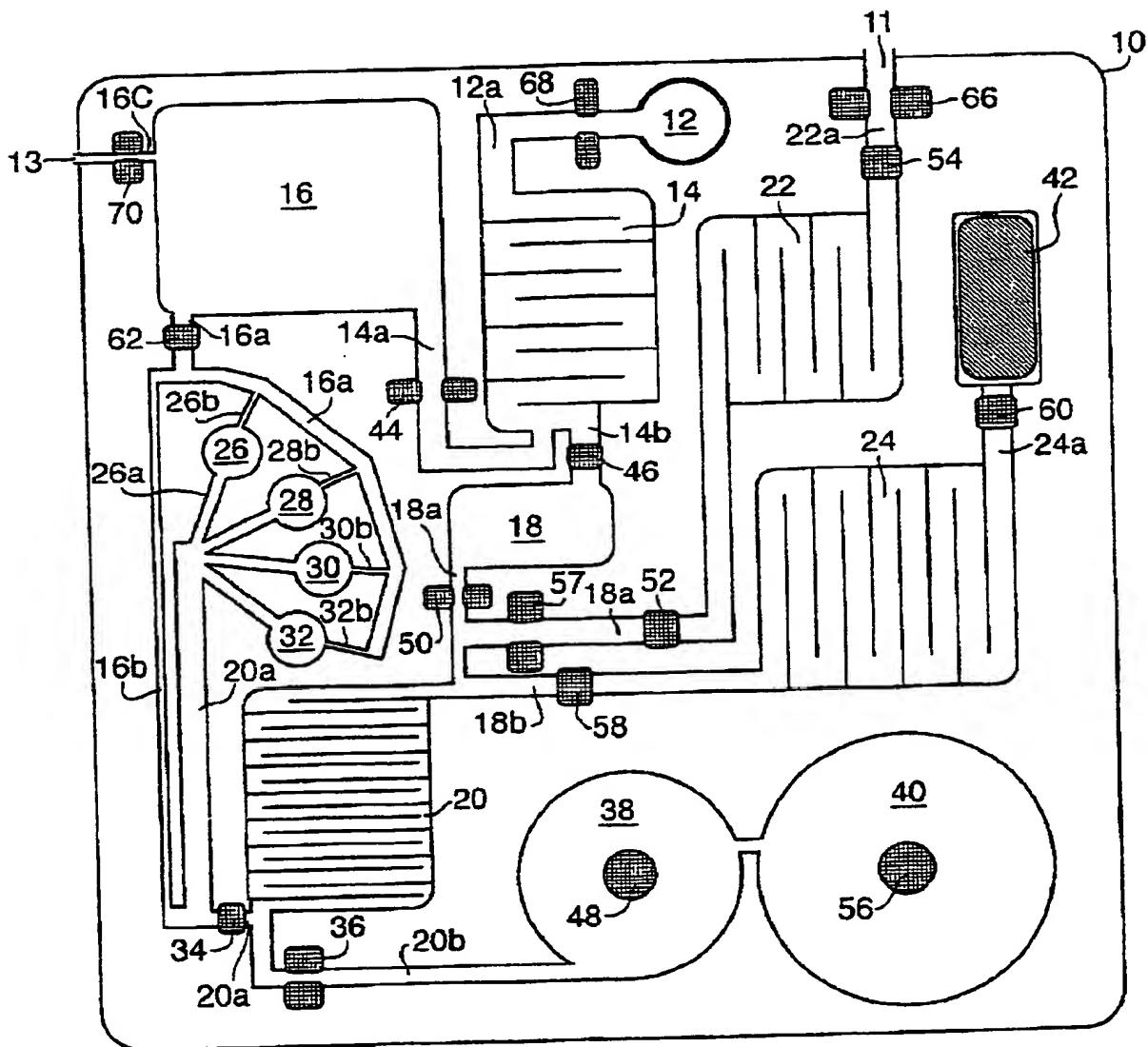
AMENDED SHEET

21a

49. An assay device (10) substantially as described with reference to Figure 1.
50. Apparatus substantially as described herein with reference to Figures 2 to 9.
51. A method of varying the rate of fluid flow along a pathway substantially as described herein with reference to the Figures.
52. A method of performing chemical analysis substantially as described with reference to the Figures.

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Fig.1.



PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference P.Q. 12,702	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/GB 99/ 00623	International filing date (day/month/year) 02/03/1999	(Earliest) Priority Date (day/month/year) 02/03/1998
Applicant CENTRAL RESEARCH LABORATORIES LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing :
 - contained in the international application in written form.
 - filed together with the international application in computer readable form.
 - furnished subsequently to this Authority in written form.
 - furnished subsequently to this Authority in computer readable form.
 - the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
 - the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. Certain claims were found unsearchable (See Box I).

3. Unity of invention is lacking (see Box II).

4. With regard to the title,

- the text is approved as submitted by the applicant.
- the text has been established by this Authority to read as follows:

5. With regard to the abstract,

- the text is approved as submitted by the applicant.
- the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

- as suggested by the applicant.
- because the applicant failed to suggest a figure.
- because this figure better characterizes the invention.

1

None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
/GB 99/00623

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 B01L3/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 B01L F16K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 267 585 A (JONES THOMAS C) 7 December 1993 see abstract; figures 1,2 see column 1, line 38 - column 2, line 19 see column 2, line 65 - column 5, line 3 ---	1-4,6-8, 11,15,16
X	US 4 949 742 A (RANDO JOSEPH F ET AL) 21 August 1990 see abstract; figure 1 see column 1, line 37 - column 2, line 54 see column 3, line 60 - column 4, line 47 ---	1,2,6-8, 14
A		3-5, 13-19, 25,27 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

11 June 1999

21/06/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
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Authorized officer

Runser, C

INTERNATIONAL SEARCH REPORT

International Application No

/GB 99/00623

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 278 079 A (GUBINSKI JULIAN ET AL) 11 January 1994 cited in the application see abstract; figures 2-5 see column 2, line 20 - column 3, line 44 see column 4, line 41 - column 5, line 43 see column 6, line 24 - column 7, line 5 see column 8, line 49 - column 9, line 19	4, 7-9, 16, 18, 22, 35
A	---	2, 17, 19, 36-39
X	US 4 549 952 A (COLUMBUS RICHARD L) 29 October 1985 see abstract; figures 1-4 see column 2, line 5 - column 2, line 42 see column 3, line 11 - column 5, line 56	4, 7-9, 16, 18, 22, 35
A	---	2, 19, 31, 36-39
X, P	WO 98 22625 A (BECTON DICKINSON CO ;REGENT OF THE UNIVERSITY OF MI (US)) 28 May 1998 see abstract; figure 1 see page 4, line 23 - page 9, line 17 see page 28, line 24 - page 29, line 2 see page 30, line 3 - page 37, line 21	2, 4, 6-9, 11, 14, 16, 18-20, 25, 27, 32, 35-39
A	-----	1, 3, 28, 31, 33

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 99/00623

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US 5267585	A 07-12-1993	NONE		
US 4949742	A 21-08-1990	NONE		
US 5278079	A 11-01-1994	NONE		
US 4549952	A 29-10-1985	CA 1211157 A DE 3376146 A EP 0110771 A JP 1747373 C JP 4030542 B JP 59105556 A	09-09-1986 05-05-1988 13-06-1984 25-03-1993 22-05-1992 18-06-1984	
WO 9822625	A 28-05-1998	AU 5265698 A		10-06-1998

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 99/00623

Patent document cited in search report	Publication date	Patent family member(s)			Publication date
US 5267585	A 07-12-1993	NONE			
US 4949742	A 21-08-1990	NONE			
US 5278079	A 11-01-1994	NONE			
US 4549952	A 29-10-1985	CA DE EP JP JP JP	1211157 A 3376146 A 0110771 A 1747373 C 4030542 B 59105556 A		09-09-1986 05-05-1988 13-06-1984 25-03-1993 22-05-1992 18-06-1984
WO 9822625	A 28-05-1998	AU	5265698 A		10-06-1998

INTERNATIONAL SEARCH REPORT

International Application No.

GB 99/00623

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 B01L3/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 B01L F16K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 267 585 A (JONES THOMAS C) 7 December 1993 see abstract; figures 1,2 see column 1, line 38 - column 2, line 19 see column 2, line 65 - column 5, line 3 ---	1-4,6-8, 11,15,16
X	US 4 949 742 A (RANDO JOSEPH F ET AL) 21 August 1990 see abstract; figure 1 see column 1, line 37 - column 2, line 54 see column 3, line 60 - column 4, line 47 ---	1,2,6-8, 14
A	---	3-5, 13-19, 25,27 -/-

Further documents are listed in the continuation of box C.

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- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art;

"&" document member of the same patent family

Date of the actual completion of the international search

11 June 1999

Date of mailing of the international search report

21/06/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
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Runser, C

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/00623

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 278 079 A (GUBINSKI JULIAN ET AL) 11 January 1994 cited in the application see abstract; figures 2-5 see column 2, line 20 - column 3, line 44 see column 4, line 41 - column 5, line 43 see column 6, line 24 - column 7, line 5 see column 8, line 49 - column 9, line 19	4,7-9, 16,18, 22,35
A	---	2,17,19, 36-39
X	US 4 549 952 A (COLUMBUS RICHARD L) 29 October 1985 see abstract; figures 1-4 see column 2, line 5 - column 2, line 42 see column 3, line 11 - column 5, line 56	4,7-9, 16,18, 22,35
A	---	2,19,31, 36-39
X,P	WO 98 22625 A (BECTON DICKINSON CO ;REGENT OF THE UNIVERSITY OF MI (US)) 28 May 1998 see abstract; figure 1 see page 4, line 23 - page 9, line 17 see page 28, line 24 - page 29, line 2 see page 30, line 3 - page 37, line 21	2,4,6-9, 11,14, 16, 18-20, 25,27, 32,35-39
A	-----	1,3,28, 31,33

PATENT COOPERATION TREATY

PCT

A/H

AH 21/09/99

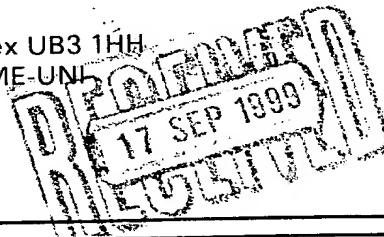
NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

From the INTERNATIONAL BUREAU

To:

WALKER, Neville, Daniel, Alan
 QED I.P. Services Limited
 Dawley Road
 Hayes
 Middlesex UB3 1HH
 ROYAUME-UNI



Date of mailing (day/month/year)
10 September 1999 (10.09.99)

Applicant's or agent's file reference
P.Q. 12,702

International application No.	International filing date (day/month/year)
PCT/GB99/00623	02 March 1999 (02.03.99)

IMPORTANT NOTICE

Priority date (day/month/year)
02 March 1998 (02.03.98)

Applicant

CENTRAL RESEARCH LABORATORIES LIMITED et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
 AU,EP,IL,JP,US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

CA,NO,RU

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on 10 September 1999 (10.09.99) under No. WO 99/44740

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a **demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland
Facsimile No. (41-22) 740.14.35

Authorized officer

J. Zahra
Telephone No. (41-22) 338.83.38

P. PCT COOPERATION TREA

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

Date of mailing (day/month/year)
01 May 2000 (01.05.00)

To:
Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

International application No.
PCT/GB99/00623

Applicant's or agent's file reference
P.Q. 12,702

International filing date (day/month/year)
02 March 1999 (02.03.99)

Priority date (day/month/year)
02 March 1998 (02.03.98)

Applicant

SHAW, John, Edward, Andrew

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

22 September 1999 (22.09.99)

in a notice effecting later election filed with the International Bureau on:

2. The election was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

S. Mafla

Facsimile No.: (41-22) 740.14.35

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

19 MAY 1999

**NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT**

(PCT Administrative Instructions, Section 411)

To:

WALKER, Neville, Daniel, Alan
 QED I.P. Services Limited
 Dawley Road
 Hayes
 Middlesex UB3 1HH
 ROYAUME-UNI

Date of mailing (day/month/year) 05 May 1999 (05.05.99)	
Applicant's or agent's file reference P.Q. 12,702	IMPORTANT NOTIFICATION
International application No. PCT/GB99/00623	International filing date (day/month/year) 02 March 1999 (02.03.99)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 02 March 1998 (02.03.98)
Applicant CENTRAL RESEARCH LABORATORIES LIMITED et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

<u>Priority date</u>	<u>Priority application No.</u>	<u>Country or regional Office or PCT receiving Office</u>	<u>Date of receipt of priority document</u>
02 Marc 1998 (02.03.98)	9804483.7	GB	04 May 1999 (04.05.99)



PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY



To:

WALKER, Neville, Daniel, Alan
QED I.P. Services Limited
Dawley Road
Hayes
Middlesex UB3 1HH
GRANDE BRETAGNE

AH

PL 11/4/00

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing
(day/month/year)

06.04.00

Applicant's or agent's file reference
P.Q. 12,702

IMPORTANT NOTIFICATION

International application No.
PCT/GB99/00623

International filing date (day/month/year)
02/03/1999

Priority date (day/month/year)
02/03/1998

Applicant

CENTRAL RESEARCH LABORATORIES LIMITED et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/ European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx. 523656 epmu d	Authorized officer Ipinazar, P
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P.Q. 12,702	FOR FURTHER ACTION		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB99/00623	International filing date (day/month/year) 02/03/1999	Priority date (day/month/year) 02/03/1998	
International Patent Classification (IPC) or national classification and IPC B01L3/00			
<p>Applicant CENTRAL RESEARCH LABORATORIES LIMITED et al.</p>			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 9 sheets, including this cover sheet.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of 10 sheets.</p>			
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input checked="" type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input checked="" type="checkbox"/> Certain observations on the international application 			

Date of submission of the demand 22/09/1999	Date of completion of this report 06.04.00
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich	Authorized officer Semino, D



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB99/00623

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

2-15 as originally filed

1,1a as received on 07/03/2000 with letter of 07/03/2000

Claims, No.:

1-52 as received on 07/03/2000 with letter of 07/03/2000

Drawings, sheets:

2/6-6/6 as originally filed

1/6 as received on 07/03/2000 with letter of 07/03/2000

2. The amendments have resulted in the cancellation of:

- the description, pages:
 the claims, Nos.:
 the drawings, sheets:

3. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- the entire international application.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB99/00623

- claims Nos. 49-52.

because:

- the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

- the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 49-52 are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

- the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 2-4,6,7,9,11-13,16-24,28,30,31,35-38,43,45-48
	No:	Claims 1,5,8,10,14,15,25-27,29,32-34,39-42,44
Inventive step (IS)	Yes:	Claims 7,18,19,31,36-38,43,45-48
	No:	Claims 1-6,8-17,20-30,32-35,39-42,44

Industrial applicability (IA)	Yes:	Claims 1-48
	No:	Claims

2. Citations and explanations

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB99/00623

VI. Certain documents cit'd

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

**Non-establishment of opinion with regard to novelty, inventive step and
industrial applicability**

1. Claims 49-52 are 'omnibus claims', which are not admissible under Rule 6.2(a) PCT (see also the PCT Guidelines, III-4.10). Reference to the drawings in the claims is permitted only where absolutely necessary; such is not the case here. The claims should be cancelled.
No opinion, therefore, is established with regards to the subject-matter of claims 49-52.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Relevance of the prior art

- 1.1 Document D1 (US-A-5267585) discloses (cf. claim 1, summary of the invention and Figures 1,2) a method and apparatus for controlling the flow in a flow path by means of a deformable elastomeric element, which is contained at least partially within the path and partially in a recess (cf. Figure 1). By application of a force through a control means, the flow can be prevented and, upon release of the force, the flow can be increased (cf. col. 1, l. 64 to col. 2, l. 19).
- 1.2 Document D2 (US-A-4949742) discloses (cf. claims 1,10 and Figure 1) a temperature operated gas valve (and a method for operating it), operable between two volumes (chambers), comprising a conduit between the two volumes and a meltable solid material within a restriction, which, upon heating, allows gas to pass from the first to the second volume and, when the pressure differential between the two volumes becomes small, returns to its initial position by surface tension, where it re-solidify after heating has been discontinued.
- 1.3 Document D3 (US-A-5278079) discloses (cf. claims 1,12,22 and Figures 2,3) a device for sealing a chamber by means of aqueous expandable polymer in a reduced chamber portion which forms a seal in said reduced chamber portion

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/00623

upon contact of the polymer with an aqueous medium, and a method for inhibiting the flow by means of such a device.

- 1.4 Document D4 (US-A-4549952) discloses (cf. claims 1,2 and Figures 1-4) a liquid transport device for transporting two different aqueous liquids within a capillary passage comprising control means on a surface for increasing the viscosity of the liquid flowing past that surface, wherein said control means comprises a water-swellable composition disposed on that surface, whereby the increase in viscosity causes a change in the flow of the liquid. Chambers are provided at the sides of the passage.

2. Conclusions

- 3.1 Before assessing novelty and inventive steps of the subject-matter of the claims over the available art, it is pointed out that many of the claims of the present application are drawn up in such general terms to include embodiments very different from what is detailed in the description and which can be found in very different fields including normal life activities. For example, a rubber tube for delivery of water from a reservoir falls under the definition of claim 1, since the rubber tube itself is of deformable material and upon any pressure in any point of the tube itself the fluid flow behaviour is changed.
- 3.2 In this respect, it is also important to notice that general functional or use terms, such as '**assay**' device in claim 1, do not add any structural peculiarities to the device other than those specified by the physical features of the device itself. This is true also for other terms such as '**reaction**' chamber in claims 14,20,22, insofar as any chamber in use can be used as a reaction chamber, and '**substrate**' in claims 20,23,24, which may refer to any kind of substrate.
- 3.3 In what follows, novelty and inventive steps will be established over the cited prior art. It will be apparent that very different devices in the prior art may fall under the wording of many claims of the present application.
- 4.1 The subject-matter of claims 25,26,29,33,34,39,40,41,42,44(with regard to pressure) is not novel with respect to D1 (Article 33(2) PCT).

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/00623

- 4.2 The subject-matter of claims 1,5,8,10,15,25,26,27,32,41,42,44 (with regard to heat) is not novel with respect to D2 (Article 33(2) PCT).
- 4.3 The subject-matter of claims 1,5,14 (with regard to inlet port and reaction chamber), 25,27,34,42 is not novel with respect to D3 (Article 33(2) PCT).
- 4.4 The subject-matter of claims 1,5,14 (with regard to inlet port and reaction chamber), 25,27,34,42 is not novel with respect to D4 (Article 33(2) PCT).
- 5.1 The connection of a device as the one in D1 to a chamber does not involve an inventive step (to what else should the skilled man connect such an apparatus?). Therefore the subject-matter of claims 2,3,9,17 does not involve an inventive step (Article 33(3) PCT).
- 5.2 The choice of a particular polymer as in claim 35 appears as just one of many alternative possibilities of material selection. The subject-matter of claim 17 is, therefore, not inventive (Article 33(3) PCT).
- 5.3 A device including a fluid pathway on a substrate, a chamber, one component of deformable material and two substrates bonded together is already disclosed in D3 (cf. Figure 2) and D4 (cf. Figure 2). The method of manufacturing such a device with the common activities listed in claim 20 is, therefore, not inventive either (Article 33(3) PCT).
- 5.4 Also the techniques mentioned in claims 21-24 for forming the different components are common in the field of microfabricated devices. Claims 21-24, therefore, also lack an inventive step (Article 33(3) PCT).
6. There are no examples in the description of changing the state of the deformable material other than by applying heat or pressure. It is not apparent whether or how the skilled man could carry out all the embodiments of claims 33 and 44 (and all dependent thereon) (e.g. by non exemplified UV radiation, light, ultrasonic energy) without undue burden (Article 5 PCT).
7. The additional features in claims 4,6,11,12,13,16,28,30 are not disclosed as such

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/00623

in the cited prior art. However, it is not apparent from the present application which technical problem they are designed to solve so as to provide the required inventive step (Article 33(3) PCT).

8. The inclusion of a hydrophobic region as in the apparatuses and methods of claims 7,31,43 (and also 18,19,36-38,45-48 see also Item VIII) so as to provide a path along which the deformable material is guided is not disclosed in the prior art, nor it appears to be obvious to the skilled man. The correspondent claims appear, therefore, to involve the required inventive step (Article 33(3) PCT).

Re Item VI
Certain documents cited

1. Document D5 (WO-A-9822625) was filed on 19.11.1997 claiming a priority of 20.11.1996 and published on 28.05.1998. Therefore, it is not part of the prior art (Rule 64(1) PCT); however, it can become part of the state of the art for the examination of novelty at least in the regional phase of the application (e.g. under Article 54(3) EPC).
 - 1.1 Document D5 discloses (cf. p. 9, l. 11-17; p. 32; p. 33; p. 63, chapter IV) devices and methods for sealing of channels with meltable material and the use of such sealed valves to control fluid flow. By application of heat, the meltable material at least partially liquefies and flows over areas of the valve seat and optionally of other auxiliary components (e.g. a diaphragm) so that upon subsequent cooling the valve is sealed. The meltable material may be disposed within a side channel and may be polymer. The valves are used inside microfabricated devices for amplifying nucleic acid target sequences (cf. field of the invention) including various reacting chambers and substrates (see e.g. Figure 1). Hydrophobic regions are used to direct the flow of the treated fluids along the transport channels (cf. e.g. p. 5, last par.; p. 9, l. 18 to p. 10, l. 25).
 - 1.2 The subject-matter of claims 1,2,3,8,10,14,15,25,26,27,29,32,34,40,42,44 (with regard to heat) at least would not be novel with respect to D5 under said Article 54(3) EPC.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/00623

Re Item VIII

Certain observations on the international application

1. Claims 1,2 do not satisfy the requirements of Article 6 PCT as far as conciseness is concerned, since they could be made dependent on claims 25,26.
Claims 18,19,36-38,45-48 do not satisfy the requirements of Article 6 PCT as far as conciseness is concerned, since they are superfluous with respect to claims 7,31,43(restated as dependent on claims 39-42) respectively.
2. The term 'substantially' used in claims 1,2,3,4,19 has a relative meaning (how much?) and cannot clearly establish the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT).